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(54) Title: TUMOR MARKERS IN OVARIAN CANCER

(57) Abstract: The present invention features methods of diagnosing and prognosticating ovarian tumors by detecting increased expression of an ovarian tumor marker gene in a subject or in a sample from a subject. Also featured are kits for the aforementioned diagnostic and prognostic methods. In addition, the invention features methods of treating and preventing ovarian tumors, and methods of inhibiting the growth or metastasis of ovarian tumors, by modulating the production or activity of an ovarian tumor marker polypeptide. Further featured are methods of inhibiting the growth or metastasis of an ovarian tumor by contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide.



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## TUMOR MARKERS IN OVARIAN CANCER

This invention was made with intramural support from the National Institutes of Health. The government has certain rights in the invention.

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### FIELD OF THE INVENTION

This invention relates generally to the identification of ovarian tumor markers and diagnostic, prognostic, and therapeutic methods for their use, as well as kits for use in the aforementioned methods.

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### BACKGROUND OF THE INVENTION

Ovarian cancer is one of the most common forms of neoplasia in women. Early diagnosis and treatment of any cancer ordinarily improves the likelihood of survival. However, ovarian cancer is difficult to detect in its early stages, and remains the leading cause of death among women with cancer of the female reproductive tract.

The low survival rate of ovarian cancer patients is in part due to the lack of good diagnostic markers for the detection of early stage neoplasms, and in part due to a deficit in the general understanding of ovarian cancer biology, which would facilitate the development of effective anti-tumor therapies. The present invention overcomes these shortcomings by providing much-needed improvements for the diagnosis, treatment, and prevention ovarian tumors, based on the identification of a series of ovarian tumor marker genes that are highly expressed in ovarian epithelial tumor cells and are minimally expressed in normal ovarian epithelial cells. Over 75% of all ovarian tumors, and about 95% of all malignant ovarian tumors, arise from the ovarian surface epithelium (OSE). Because the tumor marker genes are broadly expressed in various types of ovarian epithelial tumors, the present invention should greatly improve the diagnosis and treatment of most ovarian cancers.

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### SUMMARY OF THE INVENTION

In a first aspect, the invention features a method of detecting an ovarian tumor in a subject. The method includes the step of measuring the expression level of an

ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in the subject.

5           In a second aspect, the invention features a method of identifying a subject at increased risk for developing ovarian cancer. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject  
10       not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.

          In a preferred embodiment of the second aspect of the invention, the expression level of the ovarian tumor marker gene in the subject is compared to the expression level of the tumor marker gene in a reference subject that is identified as having an  
15       increased risk for developing ovarian cancer.

          In a third aspect, the invention features a method of determining the effectiveness of an ovarian cancer treatment in a subject. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject after treatment of the subject, wherein a modulation in the expression level of the ovarian  
20       tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in the subject prior to treatment, indicates an effective ovarian cancer treatment in the subject.

          In a preferred embodiment of the first three aspects of the invention, the expression level of the ovarian tumor marker gene is determined in the subject by  
25       measuring the expression level of the tumor marker gene in a sample from the subject. The sample may be, for example, a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, or serum. In another preferred embodiment of the first three aspects of the invention, the expression level of the tumor marker gene is measured *in vivo* in the subject.

30           In yet another preferred embodiment of the first three aspects of the invention, the expression level of more than one ovarian tumor marker gene is measured. For

example, the expression level of two, three, four, five, or more tumor marker genes may be measured.

In various other embodiments of the first three aspects of the invention, the expression level of the tumor marker gene may be determined by measuring the level of ovarian tumor marker mRNA. For example, the level of ovarian tumor marker mRNA may be measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization. In addition, or alternatively, the expression level of the ovarian tumor marker gene may be determined by measuring the level of ovarian tumor marker polypeptide encoded by the ovarian tumor marker gene. For example, the level of ovarian tumor marker polypeptide may be measured by ELISA, immunoblotting, or immunohistochemistry. The level of ovarian tumor marker polypeptide may also be measured *in vivo* in the subject using an antibody that specifically binds an ovarian tumor marker polypeptide, coupled to a paramagnetic label or other label used for *in vivo* imaging, and visualizing the distribution of the labeled antibody within the subject using an appropriate *in vivo* imaging method, such as magnetic resonance imaging.

In still another embodiment of the first three aspects of the invention, the expression level of the tumor marker gene may be compared to the expression level of the tumor marker gene in a reference subject diagnosed with ovarian cancer.

In a fourth aspect, the invention features a method of identifying a tumor as an ovarian tumor. The method includes the step of measuring the expression level of an ovarian tumor marker gene in a tumor cell from the tumor, wherein an increase in the expression level of the ovarian tumor marker gene in the tumor cell, relative to the expression level of the ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

In a fifth aspect, the invention features a method of treating or preventing an ovarian tumor in a subject. The method includes the step of modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in the subject.

In a sixth aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject. The method includes the step of



modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in the ovarian tumor cell in the subject.

In a seventh aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor in a subject. The method includes the step of contacting  
5 an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of the antibody to the ovarian tumor marker polypeptide inhibits the growth or metastasis of the ovarian tumor in the subject.

In various preferred embodiments of the seventh aspect of the invention, the  
10 ovarian tumor marker polypeptide may be on the surface of the ovarian tumor cell, and the antibody may be coupled to a radioisotope or to a toxic compound.

In an eighth aspect, the invention features a kit including an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

In a ninth aspect, the invention features a kit including a nucleic acid for  
15 measuring the expression level of an ovarian tumor marker gene in a subject.

In a tenth aspect, the invention features a method of diagnosing ovarian cancer in a subject. The method includes the step of measuring the amount of an ovarian tumor marker polypeptide in the subject, wherein an amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide  
20 measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

In various embodiments of the tenth aspect of the invention, the ovarian tumor marker polypeptide can be present at the surface of a cell (e.g., a cell-surface-localized polypeptide such as a cell adhesion molecule), or the ovarian tumor marker polypeptide  
25 may be in soluble form (e.g., secreted from a cell, released from a lysed cell, or otherwise detectable in a fluid-based assay).

In a preferred embodiment of all of the above aspects of the invention, the ovarian tumor may be an epithelial ovarian tumor. The epithelial ovarian tumor may be, for example, a serous cystadenoma, a borderline serous tumor, a serous  
30 cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated

carcinoma, a cystadenofibroma, an adenofibroma, or a Brenner tumor. The epithelial ovarian tumor may also be a clear cell adenocarcinoma.

In preferred embodiments of all of the above aspects of the invention, the ovarian tumor marker gene can be, but is not limited to, alpha prothymosin; beta polypeptide 2-like G protein subunit 1; tumor rejection antigen-1 (gp96)1; HSP90; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67. The ovarian tumor marker gene may also be HSP60 or Lutheran blood group (B-CAM). In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene may also be HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

The ovarian tumor marker gene may also be HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM\_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-lib) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

In still other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

In yet other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

Additional advantages of the invention will be set forth in part in the description  
5 which follows, and in part will be obvious from the description, or may be learned by  
practice of the invention. The advantages of the invention will be realized and attained  
by means of the elements and combinations particularly pointed out in the appended  
claims. It is to be understood that both the foregoing general description and the  
following detailed description are exemplary and explanatory only and are not  
10 restrictive of the invention, as claimed.

### DETAILED DESCRIPTION OF THE INVENTION

The low survival rate of ovarian cancer patients is in part due to the lack of  
good diagnostic markers allowing early detection of the disease. Further compounding  
15 this difficulty in early diagnosis is the lack of effective treatments for ovarian cancer,  
development of which has been impeded by a deficit in the general understanding of  
ovarian cancer biology. The present invention overcomes these deficits in the art by  
providing ovarian tumor markers that are expressed at elevated levels in ovarian  
epithelial tumor cells, relative to their expression in normal ovarian epithelial cells.

20 To identify marker genes that are up-regulated in ovarian tumor cells, SAGE  
(Serial Analysis of Gene Expression; Velculescu et al., *Science* 270:484-487, 1995)  
was employed to obtain global gene expression profiles of three ovarian tumors, five  
ovarian tumor cell lines of various histological types, a pool of ten ovarian tumor cell  
lines of various histological types, and normal human ovarian surface epithelium  
25 (HOSE). The expression patterns were generated by acquiring thousands of short  
sequence tags that contain sufficient information to uniquely identify transcripts due to  
the unique position of each tag within the transcript. Comparing the SAGE-generated  
expression profiles between ovarian cancer and HOSE revealed an abundance of genes  
that are expressed at elevated levels in ovarian tumor cells, relative to their expression  
30 in normal HOSE.

Selected SAGE results were further validated through immunohistochemical analysis of archival ovarian serous carcinoma samples. Ovarian tumor marker genes implicated in immune response pathways, regulation of cell proliferation, and protein folding were identified, many of which are membrane-localized or secreted. The ovarian tumor marker genes identified from these SAGE profiles are useful both as diagnostic and prognostic markers to detect and monitor a broad variety of ovarian cancers, and as therapeutic targets for the treatment of such ovarian cancers.

### Definitions

10 In this specification and in the claims that follow, reference is made to a number of terms that shall be defined to have the following meanings.

As used in the specification and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. For example, “a cell” can mean a single cell or more than one cell.

15 By “ovarian cell” is meant a cell that is of ovarian origin or that is a descendent of a cell of ovarian origin (e.g., a metastatic tumor cell in the liver that is derived from a tumor originating in the ovary), irrespective of whether the cell is physically within the ovary at the time at which it is subjected to a diagnostic test or an anti-tumor treatment. For example, the ovarian cell may be a normal ovarian cell or an ovarian tumor cell, 20 either within the ovary or at another location within the body. The ovarian cell may also be outside the body (for example, in a tissue biopsy). A preferred ovarian cell is an ovarian cell of epithelial origin.

By “ovarian tumor marker gene” is meant a gene of the invention, for which expression is increased (as described below) in ovarian tumor cells relative to normal ovarian cells. Preferably, an ovarian tumor marker gene has been observed to display 25 increased expression in at least two ovarian tumor SAGE libraries (relative to a HOSE library), more preferably in at least three SAGE libraries, and most preferably in at least four SAGE libraries (relative to a HOSE library). Examples of ovarian tumor marker genes are provided in Tables 2 and 4 hereinbelow.

30 By “ovarian tumor marker polypeptide” is meant a polypeptide that is encoded by an ovarian tumor marker gene and is produced at an increased level in an ovarian

tumor cell due to the increased expression of the ovarian tumor marker gene that encodes the polypeptide.

By "sample" is meant any body fluid (e.g., but not limited to, blood, serum, urine, cerebrospinal fluid, semen, sputum, saliva, tears, joint fluids, body cavity fluids (e.g., peritoneal fluid), or washings), tissue, or organ obtained from a subject; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a lysate (or lysate fraction) or extract derived from a cell; or a molecule derived from a cell or cellular material.

By "modulate" is meant to alter, by increase or decrease.

By "increase in gene expression level," "expressed at an increased level," "increased expression," and similar phrases is meant a rise in the relative amount of mRNA or protein, e.g., on account of an increase in transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is augmented. Preferably the increase is by at least about 3-fold, more preferably, by at least about: 4-fold, 5-fold, 7-fold, 10-fold, 15-fold, 20-fold, 30-fold, 40-fold, 50-fold, 70-fold, or more. For example, as described herein, the expression level of the ovarian tumor marker genes of the invention is generally increased by at least 3-fold in ovarian tumor cells, relative to normal ovarian surface epithelial cells.

By "decrease in gene expression level" is meant a reduction in the relative amount of mRNA or protein transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is reduced. Preferably the decrease is by at least about 20%-25%, more preferably by at least about 26%-50%, still more preferably by at least about 51%-75%, even more preferably by at least about 76%-95%, and most preferably, by about 96%-100%.

By "about" is meant  $\pm 10\%$  of a recited value.

By "modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene" is meant to increase or decrease gene expression level, as described above, or to stimulate or inhibit the ability of an ovarian tumor marker polypeptide to perform its intrinsic biological function (examples of such functions include, but are

not limited to, enzymatic activity, e.g., kinase activity or GTPase activity; cell-signaling activity, e.g., activation of a growth factor receptor; or cell adhesion activity. The modulation may be an increase in the amount of the polypeptide produced or an increase in the activity of the polypeptide, of at least about: 2-fold, 4-fold, 6-fold, or 10-fold, or the modulation may be a decrease in the amount of the polypeptide produced or a decrease in the activity of the polypeptide, of at least about: 20%-25%, 26%-50%, 51%-75%, 76%-95%, or 96%-100%. These increases and/or decreases are compared with the amount of production and/or activity in a normal cell, sample, or subject.

By "effective amount" of a compound as provided herein is meant a nontoxic but sufficient amount of the compound to provide the desired effect, e.g., modulation of ovarian tumor marker gene expression or modulation of ovarian tumor marker polypeptide activity. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity and type of disease that is being treated, the particular compound used, its mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with a molecule or compound of the invention (e.g., an antibody or nucleic acid molecule) without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

By "having an increased risk" is meant a subject that is identified as having a higher than normal chance of developing an ovarian tumor, compared to the general population. Such subjects include, for example, women that have a hereditary disposition to develop ovarian cancer, for example, those identified as harboring one or more genetic mutations (e.g., a mutation in the BRCA-1 gene) that are known indicators of a greater than normal chance of developing ovarian cancer, or who have a familial history of ovarian cancer. In addition, a subject who has had, or who currently has, an ovarian tumor is a subject who has an increased risk for developing an ovarian

tumor, as such a subject may continue to develop new tumors. Subjects who currently have, or who have had, an ovarian tumor also have an increased risk for ovarian tumor metastases.

By "treat" is meant to administer a compound or molecule of the invention to a  
5 subject in order to: eliminate an ovarian tumor or reduce the size of an ovarian tumor or the number of ovarian tumors in a subject; arrest or slow the growth of an ovarian tumor in a subject; inhibit or slow the development of a new ovarian tumor or an ovarian tumor metastasis in a subject; or decrease the frequency or severity of symptoms and/or recurrences in a subject who currently has or who previously has had  
10 an ovarian tumor.

By "prevent" is meant to minimize the chance that a subject will develop an ovarian tumor or to delay the development of an ovarian tumor. For example, a woman at increased risk for an ovarian tumor, as described above, would be a candidate for therapy to prevent an ovarian tumor.

15 By "specifically binds" is meant that an antibody recognizes and physically interacts with its cognate antigen and does not significantly recognize and interact with other antigens.

By "probe," "primer," or "oligonucleotide" is meant a single-stranded DNA or RNA molecule of defined sequence that can base-pair to a second DNA or RNA  
20 molecule that contains a complementary sequence (the "target"). The stability of the resulting hybrid depends upon the extent of the base-pairing that occurs. The extent of base-pairing is affected by parameters such as the degree of complementarity between the probe and target molecules, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as  
25 temperature, salt concentration, and the concentration of organic molecules such as formamide, and is determined by methods known to one skilled in the art. Probes or primers specific for ovarian tumor marker nucleic acids (e.g., genes and/or mRNAs) preferably have at least 50%-55% sequence complementarity, more preferably at least 60%-75% sequence complementarity, even more preferably at least 80%-90%  
30 sequence complementarity, yet more preferably at least 91%-99% sequence complementarity, and most preferably 100% sequence complementarity to the ovarian

tumor marker nucleic acid to be detected. Probes, primers, and oligonucleotides may be detectably-labeled, either radioactively, or non-radioactively, by methods well-known to those skilled in the art. Probes, primers, and oligonucleotides are used for methods involving nucleic acid hybridization, such as: nucleic acid sequencing, reverse transcription and/or nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, Northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA).

By "specifically hybridizes" is meant that a probe, primer, or oligonucleotide recognizes and physically interacts (i.e., base-pairs) with a substantially complementary nucleic acid (e.g., an ovarian tumor marker mRNA of the invention) under high stringency conditions, and does not substantially base pair with other nucleic acids.

By "high stringency conditions" is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO<sub>4</sub>, pH 7.2, 7% SDS, 1 mM EDTA, and 1 % BSA (fraction V), at a temperature of 65° C, or a buffer containing 48% formamide, 4.8X SSC, 0.2 M Tris-Cl, pH 7.6, 1X Denhardt's solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42° C (these are typical conditions for high stringency Northern or Southern hybridizations). High stringency hybridization is relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to Northern and Southern hybridizations, these techniques are usually performed with relatively short probes (e.g., usually 16 nucleotides or longer for PCR or sequencing, and 40 nucleotides or longer for *in situ* hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and may be found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997, herein incorporated by reference.



Examples of ovarian tumor marker genes

Examples of ovarian tumor marker genes of the invention include alpha prothymosin (e.g., Genbank Accession No. M14483; SEQ ID NOs: 1 and 2); beta polypeptide 2-like G protein subunit 1 (e.g., Genbank Accession No. M24194; SEQ ID NOs: 3 and 4); tumor rejection antigen-1 (gp96)1 (e.g., Genbank Accession No. NM\_003299; SEQ ID NOs: 7 and 8); HSP90 (e.g., Genbank Accession No. AA071048; SEQ ID NOs: 9 and 10); Hepatoma-Derived Growth Factor (HGDF) (e.g., Genbank Accession No. D16431; SEQ ID NOs: 13 and 14); DKFZp5860031 (e.g., Genbank Accession No. AL117237; SEQ ID NOs: 15 and 16); CD63 antigen (melanoma 1 antigen) (e.g., Genbank Accession No. AA041408; SEQ ID NOs: 17 and 18); protein kinase C substrate 80K-H (e.g., Genbank Accession No. J03075; SEQ ID NOs: 19 and 20); Polymerase II cofactor 4 (PC4) (e.g., Genbank Accession No. X79805; SEQ ID NOs: 21 and 22); mitochondrial Tu translation elongation factor (e.g., Genbank Accession No. L38995; SEQ ID NOs: 23 and 24); hNRP H1 (e.g., Genbank Accession No. L22009; SEQ ID NOs: 25 and 26); Solute carrier family 2 (e.g., Genbank Accession No. AF070544; SEQ ID NOs: 27 and 28); KIAA0591 protein (e.g., Genbank Accession No. AB011163; SEQ ID NOs: 29 and 30); X-ray repair protein (e.g., Genbank Accession No. AF035587; SEQ ID Nos: 31 and 32); DKFZP564M2423 protein (e.g., Genbank Accession No. BC003049; SEQ ID NOs: 35 and 139); growth factor-regulated tyrosine kinase substrate (e.g., Genbank Accession No. D84064; SEQ ID NOs: 36 and 37); and/or eIF-2-associated p67 (e.g., Genbank Accession No. U29607; SEQ ID NOs: 38 and 39). The ovarian tumor marker gene may also be HSP60 (e.g., Genbank Accession No. M22382; SEQ ID NOs: 11 and 12) and Lutheran blood group protein (B-CAM) (e.g., Genbank Accession No. NM\_005581; SEQ ID NOs: 5 and 6).

Other examples of ovarian tumor marker genes of the invention include HLA-DR alpha chain (e.g., Genbank Accession No. K01171; SEQ ID NOs: 40 and 41); cysteine-rich protein 1 (e.g., Genbank Accession No. NM\_001311; SEQ ID NOs: 42 and 43); claudin 4 (e.g., Genbank Accession No. NM\_001305; SEQ ID NOs: 44 and 45); HOST-2 (e.g., SEQ ID NO: 46); claudin 3 (e.g., Genbank Accession No. NM\_001306; SEQ ID NOs: 47 and 48); ceruloplasmin (ferroxidase) (e.g., Genbank

Accession No. M13699; SEQ ID NOs: 49 and 50); glutathione peroxidase 3 (e.g., Genbank Accession No. D00632; SEQ ID NOs: 51 and 52); secretory leukocyte protease inhibitor (e.g., Genbank Accession No. AF114471; SEQ ID NOs: 53 and 54); HOST-1 (FLJ14303 fis) (e.g., Genbank Accession No. AK024365; SEQ ID NOs: 55 and 56); interferon-induced transmembrane protein 1 (e.g., Genbank Accession No. J04164; SEQ ID NOs: 57 and 58); apolipoprotein J/clusterin (e.g., Genbank Accession No. J02908; SEQ ID NOs: 59 and 60); serine protease inhibitor, Kunitz type 2 (e.g., Genbank Accession No. AF027205; SEQ ID NOs: 61 and 62); apolipoprotein E (e.g., Genbank Accession No. BC003557; SEQ ID NOs: 63 and 64); complement component 1, r subcomponent (e.g., Genbank Accession No. M14058; SEQ ID NOs: 65 and 66); G1P3/IFI-6-16 (e.g., Genbank Accession No. X02492; SEQ ID NOs: 67 and 68); Lutheran blood group (BCAM) (e.g., Genbank Accession No. X83425; SEQ ID NOs: 69 and 70); collagen type III, alpha-1 (e.g., Genbank Accession No. X14420; SEQ ID NOs: 71 and 72); Mal (T cell differentiation protein) (e.g., Genbank Accession No. M15800; SEQ ID NOs: 73 and 74); collagen type I, alpha-2 (e.g., Genbank Accession No. J03464; SEQ ID NOs: 75 and 76); HLA-DPB1 (e.g., Genbank Accession No. J03041; SEQ ID NOs: 77 and 78); bone marrow stroma antigen 2 (BST-2) (e.g., Genbank Accession No. D28137; SEQ ID NOs: 79 and 80); and HLA-Cw (e.g., Genbank Accession No. X17093; SEQ ID NOs: 81 and 82).

Still other examples of ovarian tumor marker genes of the invention include HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM\_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-IIb) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

Ovarian tumor marker genes of the invention may also be described by SAGE tags, as disclosed herein. For example, an ovarian tumor marker genes of the invention can include a nucleotide sequence set forth in one of SEQ ID NOs: 84-102; 103-129; or 141, 143, or 145.

Diagnostic uses of ovarian tumor marker genes and polypeptides

The ovarian tumor marker genes of the invention are overexpressed in a broad variety of ovarian epithelial tumor cells, relative to normal ovarian epithelial cells. This differential expression can be exploited in diagnostic tests for ovarian cancer, in  
5 prognostic tests for assessing the relative severity of ovarian cancer, in tests for monitoring a subject in remission from ovarian cancer, and in tests for monitoring disease status in a subject being treated for ovarian cancer. Increased expression of an ovarian tumor marker gene, i.e., detection of elevated levels of ovarian tumor marker mRNA and/or protein in a subject or in a sample from a subject (i.e., levels at least  
10 three-fold higher than in a normal subject or in an equivalent sample, e.g., blood, cells, or tissue from a normal subject) is diagnostic of ovarian cancer.

One of ordinary skill in the art will understand that in some instances, higher expression of a given ovarian tumor marker gene will indicate a worse prognosis for a subject having ovarian cancer. For example, relatively higher levels of ovarian tumor  
15 marker gene expression may indicate a relative large primary tumor, a higher tumor burden (e.g., more metastases), or a relatively more malignant tumor phenotype.

The diagnostic and prognostic methods of the invention involve using known methods, e.g., antibody-based methods to detect ovarian tumor marker polypeptides and nucleic acid hybridization- and/or amplification-based methods to detect ovarian tumor  
20 marker mRNA. One of ordinary skill in the art will understand how to choose the most appropriate method for measuring ovarian tumor marker expression, based upon the combination of the particular ovarian tumor marker to be measured, the information desired, and the particular type of diagnostic test to be used. For example, immunological tests such as enzyme-linked immunosorbent assays (ELISA),  
25 radioimmunoassays (RIA), and Western blots may be used to measure the level of an ovarian tumor marker polypeptide in a body fluid sample (such as blood, serum, sputum, urine, or peritoneal fluid). Biopsies, tissue samples, and cell samples (such as ovaries, lymph nodes, ovarian surface epithelial cell scrapings, lung biopsies, liver biopsies, and any fluid sample containing cells (such as peritoneal fluid, sputum, and  
30 pleural effusions) may be tested by disaggregating and/or solubilizing the tissue or cell sample and subjecting it to an immunoassay for polypeptide detection, such as ELISA,

RIA, or Western blotting. Such cell or tissue samples may also be analyzed by nucleic acid-based methods, e.g., reverse transcription-polymerase chain reaction (RT-PCR) amplification, Northern hybridization, or slot- or dot-blotting. To visualize the three-dimensional distribution of tumor cells within a tissue sample, diagnostic tests that preserve the tissue structure of a sample, e.g., immunohistological staining, *in situ* RNA hybridization, or *in situ* RT-PCR may be employed to detect ovarian tumor marker polypeptide or mRNA, respectively. For *in vivo* localization of tumor masses, imaging tests such as magnetic resonance imaging (MRI) may be employed by introducing into the subject an antibody that specifically binds an ovarian tumor marker polypeptide (particularly a cell surface-localized polypeptide), wherein the antibody is conjugated or otherwise coupled to a paramagnetic tracer (or other appropriate detectable moiety, depending upon the imaging method used); alternatively, localization of an unlabeled tumor marker-specific antibody may be detected using a secondary antibody coupled to a detectable moiety.

The skilled artisan will understand that selection of a particular ovarian tumor marker polypeptide as the target for detection in any diagnostic test and selection of the particular test to be employed will depend upon the type of sample to be tested. For example, measurement of ovarian tumor marker polypeptides that are secreted from a cell (e.g., HDGF) may be preferred for serological tests. Moreover, ovarian tumor marker polypeptides that are not normally actively secreted from cells (e.g., intracellular or membrane-associated polypeptides), but that are found in blood and other fluid samples (e.g., peritoneal fluid or washings) at detectable levels in subjects having tumors (e.g., due to tumor cell lysis) are considered to be soluble ovarian tumor marker polypeptides that may be used in serological and other diagnostic assays of body fluids.

A fluid sample (such as blood, peritoneal fluid, sputum, or pleural effusions) from a subject with ovarian cancer, particularly metastatic cancer, may contain one or more ovarian tumor cells or ovarian tumor cell fragments. The presence of such cells or fragments allows detection of a tumor mRNA using an RT-PCR assay, e.g., but not limited to, real-time quantitative RT-PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996).

In addition, since rapid tumor cell destruction often results in autoantibody generation, the ovarian tumor markers of the invention may be used in serological assays (e.g., an ELISA test of a subject's serum) to detect autoantibodies against ovarian tumor markers in a subject. Ovarian tumor marker polypeptide-specific  
5 autoantibody levels that are at least about 3-fold higher (and preferably at least 5-fold or 7-fold higher, most preferably at least 10-fold or 20-fold higher) than in a control sample are indicative of ovarian cancer.

Cell-surface localized, intracellular, and secreted ovarian tumor marker polypeptides may all be employed for analysis of biopsies, e.g., tissue or cell samples  
10 (including cells obtained from liquid samples such as peritoneal cavity fluid) to identify a tissue or cell biopsy as containing ovarian tumor cells. A biopsy may be analyzed as an intact tissue or as a whole-cell sample, or the tissue or cell sample may be disaggregated and/or solubilized as necessary for the particular type of diagnostic test to be used. For example, biopsies or samples may be subjected to whole-tissue or whole-  
15 cell analysis of ovarian tumor marker polypeptide or mRNA levels *in situ*, e.g., using immunohistochemistry, *in situ* mRNA hybridization, or *in situ* RT-PCR. The skilled artisan will know how to process tissues or cells for analysis of polypeptide or mRNA levels using immunological methods such as ELISA, immunoblotting, or equivalent methods, or analysis of mRNA levels by nucleic acid-based analytical methods such as  
20 RT-PCR, Northern hybridization, or slot- or dot-blotting.

All of the above methods are well-known in the art. For example, generation of antibodies against a given protein, ELISA, immunoblotting, selection of nucleic acid primers for PCR, RT-PCR, Northern hybridization, *in situ* hybridization, *in situ* RT-PCR, and slot- or dot-blotting are all well-described in *Current Protocols in Molecular*  
25 *Biology* (Ausubel et al., eds.), John Wiley and Sons, Inc., 1996.

#### Kits for measuring expression levels of ovarian tumor marker genes

The present invention provides kits for detecting an increased expression level of an ovarian tumor marker gene in a subject. A kit for detecting ovarian tumor marker  
30 polypeptide will contain an antibody that specifically binds a chosen ovarian tumor marker polypeptide. A kit for detecting ovarian tumor marker mRNA will contain one

or more nucleic acids (e.g., one or more oligonucleotide primers or probes, DNA probes, RNA probes, or templates for generating RNA probes) that specifically hybridize with a chosen ovarian tumor marker mRNA.

Particularly, the antibody-based kit can be used to detect the presence of, and/or  
5 measure the level of, an ovarian tumor marker polypeptide that is specifically bound by the antibody or an immunoreactive fragment thereof. The kit can include an antibody reactive with the antigen and a reagent for detecting a reaction of the antibody with the antigen. Such a kit can be an ELISA kit and can contain a control (e.g., a specified amount of a particular ovarian tumor marker polypeptide), primary and secondary  
10 antibodies when appropriate, and any other necessary reagents such as detectable moieties, enzyme substrates and color reagents as described above. The diagnostic kit can, alternatively, be an immunoblot kit generally comprising the components and reagents described herein.

A nucleic acid-based kit can be used to detect and/or measure the expression  
15 level of an ovarian tumor marker gene by detecting and/or measuring the amount of ovarian tumor marker mRNA in a sample, such as a tissue or cell biopsy (e.g., an ovary, ovarian cell scrapings, a bone marrow biopsy, a lung biopsy or lung aspiration, etc.). For example, an RT-PCR kit for detection of elevated expression of an ovarian tumor marker gene will contain oligonucleotide primers sufficient to perform reverse  
20 transcription of ovarian tumor marker mRNA to cDNA and PCR amplification of ovarian tumor marker cDNA, and will preferably also contain control PCR template molecules and primers to perform appropriate negative and positive controls, and internal controls for quantitation. One of ordinary skill in the art will understand how to select the appropriate primers to perform the reverse transcription and PCR reactions,  
25 and the appropriate control reactions to be performed. Such guidance is found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997. Numerous variations of RT-PCR are known in the art. One example of a quantitative RT-PCR assay is the real-time quantitative RT-PCR assay described by Heid and Stevens (*Genome Res.* 6:986-94, 1996), in which the  
30 primers are labeled by a fluorescent tag, and the amount of amplification product may be measured in a Taqman apparatus (Perkin-Elmer; Norwal, CT).

### Targeted delivery of immunotoxins to ovarian tumor cells

The tumor marker genes of the invention can be employed as therapeutic targets for the treatment or prevention of ovarian cancer. For example, an antibody molecule that specifically binds a cell surface-localized ovarian tumor marker polypeptide can be conjugated to a radioisotope or other toxic compound. Antibody conjugates are administered to the subject such that the binding of the antibody to its cognate ovarian tumor marker polypeptide results in the targeted delivery of the therapeutic compound to ovarian tumor cells, thereby treating an ovarian cancer.

The therapeutic moiety can be a toxin, radioisotope, drug, chemical, or a protein (see, e.g., Bera et al. "Pharmacokinetics and antitumor activity of a bivalent disulfide-stabilized Fv immunotoxin with improved antigen binding to erbB2" *Cancer Res.* 59:4018-4022 (1999)). For example, the antibody can be linked or conjugated to a bacterial toxin (e.g., diphtheria toxin, pseudomonas exotoxin A, cholera toxin) or plant toxin (e.g., ricin toxin) for targeted delivery of the toxin to a cell expressing the ovarian tumor marker. This immunotoxin can be delivered to a cell and upon binding the cell surface-localized ovarian tumor marker polypeptide, the toxin conjugated to the ovarian tumor marker-specific antibody will be delivered to the cell.

In addition, for any ovarian tumor polypeptide for which there is a specific ligand (e.g., a ligand that binds a cell surface-localized protein), the ligand can be used in place of an antibody to target a toxic compound to an ovarian tumor cell, as described above.

### Antibodies that specifically bind ovarian tumor marker polypeptides

The term "antibodies" is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact immunoglobulin molecules, also included in the term "antibodies" are fragments or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, so long as they exhibit any of the desired properties (e.g., specific binding of an ovarian tumor marker polypeptide, delivery of a toxin to an ovarian tumor cell expressing an ovarian tumor marker gene at an increased level, and/or inhibiting the activity of an ovarian tumor marker polypeptide) described herein.

Whenever possible, the antibodies of the invention may be purchased from commercial sources. The antibodies of the invention may also be generated using well-known methods. The skilled artisan will understand that either full length ovarian tumor marker polypeptides or fragments thereof may be used to generate the antibodies of the invention. A polypeptide to be used for generating an antibody of the invention may be partially or fully purified from a natural source, or may be produced using recombinant DNA techniques. For example, a cDNA encoding an ovarian tumor marker polypeptide, or a fragment thereof, can be expressed in prokaryotic cells (e.g., bacteria) or eukaryotic cells (e.g., yeast, insect, or mammalian cells), after which the recombinant protein can be purified and used to generate a monoclonal or polyclonal antibody preparation that specifically bind the ovarian tumor marker polypeptide used to generate the antibody.

In addition, one of skill in the art will know how to choose an antigenic peptide for the generation of monoclonal or polyclonal antibodies that specifically bind ovarian tumor antigen polypeptides. Antigenic peptides for use in generating the antibodies of the invention are chosen from non-helical regions of the protein that are hydrophilic. The PredictProtein Server ([http://www.embl-heidelberg.de/predictprotein/subunit\\_def.html](http://www.embl-heidelberg.de/predictprotein/subunit_def.html)) or an analogous program may be used to select antigenic peptides to generate the antibodies of the invention. In one example, a peptide of about fifteen amino acids may be chosen and a peptide-antibody package may be obtained from a commercial source such as Anaspec (San Jose, CA). One of skill in the art will know that the generation of two or more different sets of monoclonal or polyclonal antibodies maximizes the likelihood of obtaining an antibody with the specificity and affinity required for its intended use (e.g., ELISA, immunohistochemistry, *in vivo* imaging, immunotoxin therapy). The antibodies are tested for their desired activity by known methods, in accordance with the purpose for which the antibodies are to be used (e.g., ELISA, immunohistochemistry, immunotherapy, etc.; for further guidance on the generation and testing of antibodies, see, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988). For example, the antibodies may be tested in ELISA assays, Western blots, immunohistochemical staining of formalin-fixed



ovarian cancers or frozen tissue sections. After their initial *in vitro* characterization, antibodies intended for therapeutic or *in vivo* diagnostic use are tested according to known clinical testing methods.

The term "monoclonal antibody" as used herein refers to an antibody obtained  
5 from a substantially homogeneous population of antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies  
10 derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired antagonistic activity (See, U.S. Pat. No. 4,816,567 and *Morrison et al.*, Proc.  
15 Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

Monoclonal antibodies of the invention may be prepared using hybridoma methods, such as those described by *Kohler and Milstein*, Nature, 256:495 (1975). In a hybridoma method, a mouse or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of  
20 producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional  
25 procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can  
30 be performed using papain. Examples of papain digestion are described in WO 94/29348 published Dec. 22, 1994 and U.S. Pat. No. 4,342,566. Papain digestion of

antibodies typically produces two identical antigen binding fragments, called Fab fragments, each with a single antigen binding site, and a residual Fc fragment. Pepsin treatment yields a fragment that has two antigen combining sites and is still capable of cross-linking antigen.

5           The antibody fragments, whether attached to other sequences or not, can also include insertions, deletions, substitutions, or other selected modifications of particular regions or specific amino acids residues, provided the activity of the fragment is not significantly altered or impaired compared to the nonmodified antibody or antibody fragment. These modifications can provide for some additional property, such as to  
10   remove/add amino acids capable of disulfide bonding, to increase its bio-longevity, to alter its secretory characteristics, etc. In any case, the antibody fragment must possess a bioactive property, such as binding activity, regulation of binding at the binding domain, etc. Functional or active regions of the antibody may be identified by mutagenesis of a specific region of the protein, followed by expression and testing of  
15   the expressed polypeptide. Such methods are readily apparent to a skilled practitioner in the art and can include site-specific mutagenesis of the nucleic acid encoding the antibody fragment. (Zoller, M.J. *Curr. Opin. Biotechnol.* 3:348-354, 1992).

          The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are  
20   chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a  
25   non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues.

Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the  
30   humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to

those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (*Jones et al.*, Nature, 321:522-525 (1986), *Reichmann et al.*, Nature, 332:323-327 (1988), and *Presta*, Curr. Op. Struct. Biol., 2:593-596 (1992)).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (*Jones et al.*, Nature, 321:522-525 (1986), *Riechmann et al.*, Nature, 332:323-327 (1988), *Verhoeyen et al.*, Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production can be employed. For example, it has been described that the homozygous deletion of the antibody heavy chain joining region (J(H)) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., *Jakovovits et al.*, Proc. Natl. Acad. Sci. USA, 90:2551-2555 (1993); *Jakovovits et al.*, Nature, 362:255-258 (1993); *Bruggermann et al.*, Year in Immuno., 7:33 (1993)). Human antibodies can also be produced in phage display libraries (*Hoogenboom et al.*, J. Mol. Biol., 227:381 (1991); *Marks et al.*, J. Mol. Biol.,

222:581 (1991)). The techniques of Cote et al. and *Boerner et al.* are also available for the preparation of human monoclonal antibodies (*Cole et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985) and *Boerner et al.*, *J. Immunol.*, 147(1):86-95 (1991)].

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#### Administration of therapeutic and diagnostic antibodies

Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Suitable carriers and their formulations are described in *Remington's Pharmaceutical Sciences*, 16th ed., 1980, Mack Publishing Co., edited by Oslo et al. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of antibody being administered.

20 The antibodies can be administered to the subject, patient, or cell by injection (e.g., intravenous, intraperitoneal, subcutaneous, intramuscular), or by other methods such as infusion that ensure its delivery to the bloodstream in an effective form. The antibodies may also be administered by intratumoral or peritumoral routes, to exert local as well as systemic therapeutic effects. Local or intravenous injection is preferred.

25 Effective dosages and schedules for administering the antibodies may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of antibodies that must be administered will vary depending on, for example, the subject that will receive the antibody, the route of administration, the particular type of antibody used and other drugs being administered. Guidance in selecting appropriate doses for antibodies is found in the literature on therapeutic uses of antibodies, e.g., *Handbook of Monoclonal*

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Antibodies, Ferrone et al., eds., Nokes Publications, Park Ridge, N.J., (1985) ch. 22 and pp. 303-357; Smith et al., Antibodies in Human Diagnosis and Therapy, Haber et al., eds., Raven Press, New York (1977) pp. 365-389. A typical daily dosage of the antibody used alone might range from about 1  $\mu\text{g/kg}$  to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above.

Following administration of an antibody for treating ovarian cancer, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. For instance, the size, number, and/or distribution of ovarian tumors in a subject receiving treatment may be monitored using standard tumor imaging techniques. A therapeutically-administered antibody that arrests tumor growth, results in tumor shrinkage, and/or prevents the development of new tumors, compared to the disease course that would occur in the absence of antibody administration, is an efficacious antibody for treatment of ovarian cancer.

15 Antisense and gene therapy approaches for inhibiting ovarian tumor marker gene function

Because the ovarian tumor marker genes of the invention are highly expressed in ovarian tumor cells and are expressed at extremely low levels in normal ovarian cells, inhibition of ovarian tumor marker expression or polypeptide activity may be integrated into any therapeutic strategy for treating or preventing ovarian cancer.

The principle of antisense therapy is based on the hypothesis that sequence-specific suppression of gene expression (via transcription or translation) may be achieved by intracellular hybridization between genomic DNA or mRNA and a complementary antisense species. The formation of such a hybrid nucleic acid duplex interferes with transcription of the target tumor antigen-encoding genomic DNA, or processing/transport/translation and/or stability of the target tumor antigen mRNA.

Antisense nucleic acids can be delivered by a variety of approaches. For example, antisense oligonucleotides or antisense RNA can be directly administered (e.g., by intravenous injection) to a subject in a form that allows uptake into tumor cells. Alternatively, viral or plasmid vectors that encode antisense RNA (or RNA fragments) can be introduced into cells *in vivo*. Antisense effects can also be induced

by sense sequences; however, the extent of phenotypic changes are highly variable. Phenotypic changes induced by effective antisense therapy are assessed according to changes in, e.g., target mRNA levels, target protein levels, and/or target protein activity levels.

5 In a specific example, inhibition of ovarian tumor marker function by antisense gene therapy may be accomplished by direct administration of antisense ovarian tumor marker RNA to a subject. The antisense tumor marker RNA may be produced and isolated by any standard technique, but is most readily produced by *in vitro* transcription using an antisense tumor marker cDNA under the control of a high efficiency promoter (e.g., the T7 promoter). Administration of antisense tumor marker RNA to cells can be carried out by any of the methods for direct nucleic acid administration described below.

15 An alternative strategy for inhibiting ovarian tumor marker polypeptide function using gene therapy involves intracellular expression of an anti-ovarian tumor marker antibody or a portion of an anti-ovarian tumor marker antibody. For example, the gene (or gene fragment) encoding a monoclonal antibody that specifically binds to an ovarian tumor marker polypeptide and inhibits its biological activity is placed under the transcriptional control of a specific (e.g., tissue- or tumor-specific) gene regulatory sequence, within a nucleic acid expression vector. The vector is then administered to the subject such that it is taken up by ovarian tumor cells or other cells, which then secrete the anti-ovarian tumor marker antibody and thereby block biological activity of the ovarian tumor marker polypeptide. Preferably, the ovarian tumor marker polypeptide is present at the extracellular surface of ovarian tumor cells.

## 25 Nucleic Acid Delivery

In the methods described above which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), the nucleic acids of the present invention can be in the form of naked DNA or the nucleic acids can be in a vector for delivering the nucleic acids to the cells for inhibition of ovarian tumor marker protein expression. The vector can be a commercially available preparation, such as an adenovirus vector (Quantum Biotechnologies, Inc. (Laval,

Quebec, Canada). Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-BRL, Inc., Gaithersburg, MD), SUPERFECT (Qiagen, Inc. Hilden, Germany) and  
5 TRANSFECTAM (Promega Biotec, Inc., Madison, WI), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, CA) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, AZ).

10 As one example, vector delivery can be via a viral system, such as a retroviral vector system which can package a recombinant retroviral genome (see e.g., Pastan et al., *Proc. Natl. Acad. Sci. U.S.A.* 85:4486, 1988; Miller et al., *Mol. Cell. Biol.* 6:2895, 1986). The recombinant retrovirus can then be used to infect and thereby deliver to the infected cells antisense nucleic acid that inhibits expression of an ovarian tumor marker  
15 gene. The exact method of introducing the altered nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors (Mitani et al., *Hum. Gene Ther.* 5:941-948, 1994), adeno-associated viral (AAV) vectors (Goodman et al., *Blood* 84:1492-1500, 1994), lentiviral vectors (Naidini et al., *Science* 272:263-267,  
20 1996), pseudotyped retroviral vectors (Agrawal et al., *Exper. Hematol.* 24:738-747, 1996). Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanisms (see, for example, Schwartzenberger et al., *Blood* 87:472-478, 1996). This invention can be used in conjunction with any of these or other commonly used gene transfer methods.

25 As one example, if the antisense nucleic acid of this invention is delivered to the cells of a subject in an adenovirus vector, the dosage for administration of adenovirus to humans can range from about  $10^7$  to  $10^9$  plaque forming units (pfu) per injection but can be as high as  $10^{12}$  pfu per injection (Crystal, *Hum. Gene Ther.* 8:985-1001, 1997; Alvarez and Curiel, *Hum. Gene Ther.* 8:597-613, 1997). Ideally, a subject will receive  
30 a single injection. If additional injections are necessary, they can be repeated at six

month intervals for an indefinite period and/or until the efficacy of the treatment has been established.

Parenteral administration of the nucleic acid or vector of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. See, e.g., U.S. Patent No. 3,610,795, which is incorporated by reference herein. For additional discussion of suitable formulations and various routes of administration of therapeutic compounds, see, e.g., *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A.R. Gennaro, Mack Publishing Company, Easton, PA 1995.

#### **Example I: Identification of ovarian tumor marker genes using SAGE**

Serial Analysis of Gene Expression is a method that enables the global analysis of gene expression from a tissue of interest (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The advantages of SAGE over cDNA arrays, another method for the global analysis of gene expression, include: 1) the possibility of identifying novel genes, 2) determination of absolute levels of gene expression, which is difficult in hybridization-based techniques, and, 3) examination of gene expression as a whole instead of as a subset of genes.

#### **Construction and screening of SAGE libraries**

The SAGE technique has been described in detail (Velculescu et al., *Science* 270:484-487, 1995). The SAGE libraries disclosed herein were made as described by Velculescu, *supra*. First, total RNA was purified from the cells. Poly A+ RNA was then isolated and reverse transcription was performed using a biotinylated poly dT primer for first strand synthesis. The cDNA mixture was cut with *Nla*III and the biotinylated 3' fragments were collected using streptavidin beads. The beads were divided into two aliquots (A and B) and linkers containing PCR primer sites and a site for class II restriction enzyme *Bsm*FI were ligated to the DNA fragments attached to the



beads from samples A and B. The mixture was treated with the restriction enzyme *BsmFI*, which recognizes the site in the linker but cuts 14 bp downstream. The resulting fragments contained the linker and 10 bp of "cDNA sequence" that is referred to as "tag". The tags from samples A and B were ligated together to form ditags, which  
5 were then amplified by PCR. Any repeated ditag (tags containing the same two individual tags) are an indication of PCR bias and were eliminated by the SAGE software (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The tags were concatemerized and cloned into a sequencing vector. Sequencing revealed the identity and frequency of the different tags. As  
10 described above, the 10 bp tag is sufficient to identify cDNA and the frequency of a particular tag represents the frequency of a particular message in the population. The SAGE software developed in the laboratories of Bert Vogelstein and Kenneth Kinzler at Johns Hopkins extracts the tags from the raw sequencing data, matches the tags to the corresponding genes (present in Genbank) and makes frequency comparisons  
15 between the tags from an individual library or other libraries.

#### **Verification of ovarian tumor marker genes identified by SAGE**

The most promising candidates are selected and verified by any expression analysis method, e.g., Northern analysis or reverse transcription-polymerase chain  
20 reaction (RT-PCR). For Northern analysis, radioactive probes are generated from expressed sequence tags (ESTs) corresponding to the candidate genes and are used to hybridize to membranes containing total RNA from various ovarian cancers and controls. The candidates may also be verified by real-time PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996). Amplification primers and  
25 fluorescent probes are synthesized according to instructions from the manufacturer (Perkin-Elmer; Norwalk, CT). Quantitative PCR is performed using a PE 5700 apparatus or an analogous instrument.

#### **Sources of RNA for SAGE library construction**

30 Eleven SAGE libraries were constructed, as shown in Table 1. The human ovarian surface epithelial cell (HOSE) library was constructed using RNA from HOSE

cells that were obtained by gently scraping the ovarian surface from a hysterectomy patient followed by short-term *in vitro* culture (three passages) of the cells. Three of the ovarian tumor libraries (designated OVT6, OVT7, and OVT8) were constructed using RNA from one of three primary high grade serous adenocarcinomas. Libraries  
5 from individual ovarian tumor cell lines were generated using RNA from OV1063 (derived from an ovarian papillary adenocarcinoma; obtained from the American Type Culture Collection (ATCC; Manassas, VA; CRL-2183)); ES-2 (derived from a clear cell adenocarcinoma; from the ATCC; CRL-1978); A2780 (derived from an ovarian cancer; obtained from Dr. Vilhelm Bohr, Baltimore, MD); OVCA432 (derived from an  
10 ovarian serous cystadenocarcinoma; Bast et al., *J. Clin. Invest.* 68:1331-1337, 1981); ML10 (derived from an ovarian cystadenoma; Luo et al. *Gyn. Oncol.*, 67:277-284, 1997); or IOSE29 (simian virus 40-immortalized OSE cells; Auersperg et al., *Proc. Natl. Acad. Sci. USA* 96:6249-6254, 1999).

The pooled library was generated using RNA from a pool of 10 cell lines:  
15 A2780; BG-1 (poorly differentiated ovarian cancer; obtained from Dr. Carl Barrett, Durham, NC); ES-2; OVCA432; MDAH 2774 (endometrioid adenocarcinoma; obtained from the ATCC); and five cell lines obtained from Dr. Michael Birrer (Rockville, MD): AD10 (an adriamycin-resistant derivative of A2780); A222 (ovarian carcinoma); UCI101 (papillary ovarian adenocarcinoma); UCI107 (papillary ovarian  
20 adenocarcinoma); and A224 (ovarian carcinoma).

TABLE 1

Library	Seq	Tags (raw)	Tags	Genes	At least 2
HOSE	2,290	49,394	47,881	16,034	4,532
OVT6	2,104	43,891	41,620	18,476	4,799
OVT7	2,089	57,725	53,898	19,523	5,669
OVT8	2,076	36,813	32,494	16,363	3,815
OV1063	2,146	41,131	37,862	15,231	4,746
ES-2	1,775	36,430	35,352	14,739	3,952
A2780**	475	9,269	8,246	5,179	1,021
OVCA432	384	3,011	2,824	1,940	310
Pool	2,201	10,952	10,554	5,956	1,627
ML10	1,935	61,083	55,700	18,727	6,637
IOSE29	*	*	*	*	*
TOTAL	17,475	349,699	326,431	75,056	25,071

\* To be sequenced

\*\*Incomplete

### Results of SAGE

Eleven ovarian SAGE libraries were constructed, ten of which have been sequenced to date. The overall data are summarized in Table 1 above. For each SAGE library, Table 1 shows the number of SAGE library clones sequenced, the number of raw tags sequenced, the number of tags obtained after correction for PCR bias, the total number of genes that are represented by the corrected pool of tags, and the number of genes that were represented at least twice in the corrected pool of tags. For most libraries, 35,000-61,000 tags were obtained, yielding anywhere from 14,000-20,000 genes. In total, 75,056 genes were identified.

- 10 In order to identify genes that are up-regulated in ovarian tumors and that may serve as diagnostic markers and therapeutic targets, we compared gene expression between the normal ovarian cells (HOSE) and the cancer cells (OVT6, OVT7, OVT8, OV1063, ES2, A2780, Pool). OVCA432 was not included in this analysis because of the poor number of tags obtained from this library. We looked for genes for which expression
- 15 was absent or low (frequency smaller or equal to 2 tags per 100,000) in HOSE and at least 7- to 10-fold up-regulated in the majority of the tumor libraries, and detected a number of genes matching these criteria. Table 2 shows the libraries that were screened, the SAGE tags that were identified in the library screens, along with their corresponding genes and Genbank accession numbers, and the relative expression of
- 20 each gene in each library. Any one of these ovarian tumor marker genes may be used in the diagnostic and/or therapeutic methods of the invention.

TABLE 2

SEQ. ID NO. (Tag)	Tag	OVT8	OVT7	OVT6	A2780	OY1063	ES2	Pool	HOSE	Gene Product	Genbank
83	TCAGACGCAG	52	149	91	97	49	214	82	2	Prothymosin, alpha	M14483
84	TTATGGGATC	57	80	57	140	83	126	274	2	G protein, beta polypeptide 2-like 1	M24194
85	CCCGCCCCCG	136	166	52	22	7	0	146	2	Lutheran blood group (B-CAM)	NM_005581
86	GAGGAAGAAG	14	38	57	76	53	80	100	2	Tumor rejection antigen-1 (gp96) 1	NM_003299
87	GAAGCTTTGC	27	43	43	22	27	66	73	2	HSP90	AA071048
88	TACCAGTGTA	30	16	14	140	22	30	100	2	HSP60	M22382
89	TCTTCTCCCT	8	42	32	22	27	25	46	2	Hepatoma-Derived Growth Factor (HDGF)	D16431
90	TTGGCTTTTC	14	12	71	32	10	22	18	0	DKFZp5860031	AL117237
91	GGAAGGGAGG	30	14	16	11	12	44	55	2	CD63 antigen (melanoma 1 antigen)	AA041408
92	AAGCCAGCCC	19	17	36	22	17	27	18	2	Protein kinase C substrate 80K-H	J03075
93	TTTCAGATTG	16	26	25	32	22	19	18	0	Polymerase II cofactor 4 (PC4)	X79805
94	GCATAGGCTG	11	24	25	22	12	27	9	2	Tu translation elong. factor (mitochondrial)	L38995
95	TTTGTTAATT	30	16	16	43	17	19	18	2	hNRP H1	L22009
96	GAGACTCCTG	11	23	23	22	12	3	64	2	Solute carrier family 2	AF070544
97	CCTGTAATTC	19	10	27	32	15	8	27	2	KIAA0591 protein	AB011163
98	GTGGTGCGTG	16	10	21	11	15	19	27	2	X-ray repair protein	AF035587
99	TTGGACCTGG	11	19	9	11	27	16	18	2	ATP synthase (delta subunit)	AA524164
100	CTTAAGGATT	11	12	18	11	15	27	9	0	DKFZP564M2423 protein	BC003049
101	GTCTGTGAGA	8	17	9	22	12	22	18	0	Growth factor-regul. tyr kinase substrate	D84064
102	GAAACTGAAC	16	10	14	32	12	3	9	2	eIF-2-associated p67	U29607

**Example II: Identification of additional ovarian tumor marker genes using SAGE**

Serial Analysis of Gene Expression (SAGE) was used to generate global gene expression profiles from various ovarian cell lines and tissues, including primary cancers, ovarian surface epithelial (OSE) cells and cystadenoma cells. The profiles were used to compare overall patterns of gene expression and identify differentially expressed genes. We have sequenced a total of 385,000 tags, yielding over 56,000 genes expressed in ten different libraries derived from ovarian tissues.

In general, ovarian cancer cell lines showed relatively high levels of similarity to libraries from other cancer cell lines, regardless of the tissue of origin (ovarian or colon), indicating that these lines had lost many of their tissue specific expression patterns. In contrast, immortalized OSE (IOSE) and ovarian cystadenoma cells showed much higher similarity to primary ovarian carcinomas as compared to primary colon carcinomas. Primary tissue specimens therefore appeared to be a better model for gene expression analyses. Using the expression profiles described above and stringent selection criteria, we have identified a number of genes highly differentially expressed between non-transformed ovarian epithelia and ovarian carcinomas. Some of the genes identified are already known to be overexpressed in ovarian cancer but several represent novel candidates. Many of the genes up-regulated in ovarian cancer represent surface or secreted proteins such as Claudin-3 and -4, HE4, Mucin-1, Ep-CAM and Mesothelin. The genes encoding apolipoprotein E (ApoE) and apolipoprotein J (ApoJ), two proteins involved in lipid homeostasis are among the genes highly up-regulated in ovarian cancer. Selected SAGE results were further validated through immunohistochemical analysis of ApoJ, Claudin-3, Claudin-4 and Ep-CAM in archival material. These experiments provided additional evidence of the relevance of our findings *in vivo*.

**A) METHODS****Cell Culture and Tissue Samples**

Ovarian cancer cell lines OV1063, ES2, and MDAH 2774 were obtained from the American Type Culture Collection (Manassas, VA). Cell lines A222, AD10, UCI101 and UCI107 were obtained from Dr. Michael Birrer (Rockville, MD). Cell line A2780 was obtained from Dr. Vilhelm Bohr (Baltimore, MD). The SV40-

immortalized cell lines IOSE29 (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999) and ML10 (Luo, M. P., et al. *Gynecol. Oncol.* 67:277-284, 1997) were kindly provided by Dr. Nelly Auersperg (British Columbia, Canada) and Dr. Louis Dubeau (Los Angeles, CA), respectively. Except for IOSE29, ML-10 and HOSE-4, all cell lines were cultured in McCoy's 5A growth medium (Life Technologies, Inc, Gaithersburg, MD) supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 U/ml of Penicillin and 100 ug/ml Streptomycin). IOSE29 was cultivated in Medium 199 (Life Technologies, Inc, Gaithersburg, MD) supplemented with 5% newborn calf serum (NCS). ML10 was cultivated in MEM (Life Technologies, Inc, Gaithersburg, MD) supplemented with 10% FBS and antibiotics as above.

Three high-grade serous ovarian cancer specimens, OVT6, OVT7, and OVT8, composed of at least 80% tumor cells as determined by histopathology, were chosen for SAGE. The ovarian tumor samples were frozen immediately after surgical resection and were obtained from the Johns Hopkins gynecological tumor bank in accordance with institutional guidelines on the use of human tissue. Normal human ovarian surface epithelial (HOSE-4) cells were cultured from the right ovary of a patient undergoing hysterectomy and bilateral salpingo-oophorectomy for benign disease. The OSE cells were obtained by gently scraping the surface of the ovary with a cytobrush and grown for 2 passages in RPMI 1640 medium supplemented with 10% FBS and 10 ug/ml insulin-like growth factor (IGF).

### Serial Analysis of Gene Expression (SAGE)

Total RNA was obtained from guanidinium isothiocyanate cell lysates by centrifugation on CsCl. Polyadenylated mRNA was purified from total RNA using the Messagemaker kit (Life Technologies, Gaithersburg, MD) and the cDNA generated using the cDNA Synthesis System (Life Technologies, Gaithersburg, MD). For the "Pool" library, 100 ug of total RNA from each of 10 ovarian cancer cell lines (A222, A2780, AD10, BG-1, ES-2, MDAH 2774, OVCA432, OV1063, UCI101 and UCI107) were combined and mRNA purified. SAGE was performed essentially as described (Velculescu, V. E., et al. *Science* 270:484-487, 1995) for all the libraries except HOSE. To create the HOSE library, MicroSAGE, a modified SAGE technique developed for limited sample sizes (Datson, N. A., et al. *Nucleic Acids Res.* 27:1300-1307, 1999),

was used. Approximately  $1 \times 10^6$  OSE cells in short-term culture were lysed and the mRNA purified directly using Oligo (dT)<sub>25</sub> Dynabeads (Dyna, Norway). As part of the Cancer Genome Anatomy Project (CGAP) SAGE consortium, the SAGE libraries were arrayed at the Lawrence Livermore National Laboratories and sequenced at the

5 Washington University Human Genome Center or NISC (NIH, Bethesda, MD). The data has been posted on the CGAP website (<http://www.ncbi.nlm.nih.gov/SAGE/>) as part of the SAGEmap database (Lal, A., et al. *Cancer Res.* 59:5403-5407, 1999.).

Sequence data from each library were analyzed by the SAGE software (Velculescu, V. E., et al. *Science* 270:484-487, 1995.) to quantify tags and identify their  
 10 corresponding transcripts. The data for the colon libraries NC1, NC2, Tu98, Tu102, HCT116 and SW837 were obtained from the SAGEmap database and analyzed in the same way. Because the different libraries contained various numbers of total tags, normalization (to 100,000 tags) was performed to allow meaningful comparisons. The 10,000 most highly expressed genes in each of the 16 SAGE libraries of interest were  
 15 formatted in a Microsoft Excel spreadsheet and Pearson correlation coefficients were calculated for each pair-wise comparison using normalized tag values for each library. The value for the Pearson correlation coefficient (r) represents the degree of similarity (the strength of the relationship) between two libraries and is calculated using the following equation:

20

$$r = \frac{n(\sum xy) - (\sum x)(\sum y)}{\sqrt{[n\sum x^2 - (\sum x)^2][n\sum y^2 - (\sum y)^2]}}$$

where,  $x_i$  = number of tags per 100,000 for tag i in the first library and  $y_i$  = number of tags per 100,000 for tag i in the second library. For our purposes n equals 10,000 since 10,000 tags are compared. A dendrogram representing the hierarchical relationships between samples was then generated using hierarchical cluster analysis as described  
 25 (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). In addition, the identification of differentially expressed genes was also done using this subset of the SAGE data.

### Immunohistochemistry

Deparaffinized 5-um sections of formalin-fixed ovarian cancer specimens were  
 30 submitted to heat-induced antigen retrieval and processed using the LSAB2 system

(DAKO, Carpinteria, CA) with 3,3'-diaminobenzidine as the chromogen and a hematoxylin counterstain. Monoclonal antibody against ApoJ/Clusterin (Clone CLI-9) was obtained from Alexis Corporation (San Diego, CA) and used at a 1:500 Dilution. Monoclonal antibody against Ep-CAM (Clone 323/A3) from NeoMarkers (Fremont, CA) was used at a 1:500 dilution. Polyclonal antibodies against Claudin-3 and -4 were a generous gift from Drs. M. Furuse and S. Tsukita (Kyoto, Japan) and were used at a dilution of 1:1000.

## B) RESULTS

### 10 Ovarian SAGE library construction and analysis

Gene expression alterations that arise during malignant transformation can be identified a number of ways. We chose the unbiased, comprehensive method SAGE to create global gene expression profiles from ten different ovarian sources. The expression patterns are generated by sequencing thousands of short sequence tags that contain sufficient information to uniquely identify the corresponding transcripts (Velculescu, V. E., et al. *Science* 270:484-487, 1995). Ten different SAGE libraries were constructed and sequenced for this study (Table 3). Our libraries included two derived from OSE cells (IOSE29 and HOSE-4), one derived from immortalized cystadenoma cells (ML-10), three primary tumors (OVT-6, -7, -8) and four libraries derived from ovarian cancer cell lines (OV-1063, ES-2, A2780 and a pool of cell lines). Almost 20,000 sequencing reactions were performed yielding a total of 384,497 tags, of which, 82,533 were unique. Accounting for a SAGE tag error rate of 6.8% (due to sequencing errors; see Zhang, L., et al., *Science* 276:1268-1272, 1997), we estimate that we have identified a total of 56,387 genes expressed in ovarian tissues. Except for the A2780 cell line and the pooled lines (POOL) samples, a minimum of 12,000 genes were obtained from every library. Typically, for each library, 10% of the genes were expressed at levels of at least 0.01% and, collectively, these genes accounted for more than 50% of all the tags sequenced. Among the tags that appeared more than once, up to 95% matched to known sequences in the current Genbank nr database. For example, of the 6637 tags that appeared more than once in ML10, only 311 had no matches in the current database, excluding the EST databases.



**Table 3 Summary of SAGE library analyses**

<b>Library<sup>a</sup></b>	<b>Sequence</b>	<b>Tags<sup>b</sup></b>	<b>Unique tags<sup>c</sup></b>	<b>Genes<sup>d</sup></b>	<b>≥ 2 tags<sup>e</sup></b>
HOSE	2,290	47,881	16,034	12,778	4,532
IOSE	1,912	47,549	18,004	14,771	5,681
ML10	1,935	55,700	18,727	14,939	6,637
OVT6	2,104	41,620	18,476	15,646	4,799
OVT7	2,089	53,898	19,523	15,858	5,669
OVT8	2,076	32,494	16,363	14,153	3,815
OV1063	2,146	37,862	15,231	12,656	4,746
A2780	1,332	21,587	10,717	9,249	2,761
ES2	1,775	35,352	14,739	12,335	3,952
POOL	2,201	10,554	5,956	5,238	1,627
<b>TOTAL</b>	<b>19,860</b>	<b>384,497</b>	<b>82,533</b>	<b>56,387</b>	<b>28,219</b>

<sup>a</sup>The libraries are: HOSE, human ovarian surface epithelium from short term culture; IOSE, SV40-immortalized ovarian surface epithelium; ML10, SV40-immortalized benign cystadenoma; OVT6, OVT7, and OVT8, primary ovarian serous adenocarcinomas; OV1063, A2780, and ES2, ovarian cancer cell lines; POOL, a pool of ten ovarian cancer cell lines.

<sup>b</sup>Tag numbers after elimination of linker-based tags and duplicate ditags.

<sup>c</sup>The number of unique tags identified in each library.

<sup>d</sup>The number of genes identified after correction for sequencing errors.

<sup>e</sup>The number of genes represented at least twice.

### Comparisons of global gene expression between ovarian tissue samples

Although progression to malignancy requires a number of gene expression changes, the transcript levels from the vast majority of genes remain unaltered (Zhang, L., et al., *Science* 276:1268-1272, 1997; and Alon, U., et al., *Proc. Natl Acad. Sci. USA* 96:6745-6750, 1999). Similarities between the global expression profiles of two given samples can be readily visualized using scatterplots and quantitated through the calculation of Pearson correlation coefficients. Scatterplots of global gene expression analysis in IOSE (ovarian) vs. ML10 (ovarian), OVT6 (ovarian), or Tu98 (colon) cells were generated using the Spotfire Pro 4.0 software (Cambridge, MA) and the Pearson correlation coefficients for each pair-wise comparison of the 16 ovarian and colon SAGE libraries were calculated.

As expected, the immortalized IOSE29 and ovarian cystadenoma strain ML10 are much more similar to ovarian tumors than to colon tumors (average correlation coefficients of 0.70 vs. 0.51, respectively). In addition, IOSE29 and ML10 are very similar to each other, with a correlation coefficient of 0.82. The primary culture of OSE cells (HOSE-4) exhibited higher similarities to the ovarian tumors than to the colon tumors, although the similarity levels were much lower than those observed for IOSE29. Interestingly, HOSE-4 and IOSE29 appear to be much more distantly related than expected considering the fact that they were both derived from "normal" OSE cells. The differences in gene expression between these cells may be due to a number of factors. The age of the patient, the pathological state of the ovaries, the presence of non-epithelial cells in the culture and the fact that IOSE29 is SV40-immortalized may all contribute to the gene expression differences observed. However, it is unlikely that the main differences are due to SV40-immortalization since IOSE29 is much more similar to normal colon (a non SV40-immortalized epithelium) than HOSE-4. It is, of course, possible that the lower degree of similarity between HOSE-4 and the ovarian tumors compared to IOSE29 and ML-10 reflects the fact that HOSE-4 represents a better approximation of the normal *in vivo* OSE cell.

Three dendrograms were created from hierarchical cluster analysis of all colon and ovarian SAGE libraries, ovarian samples only, and non-malignant ovarian and colon epithelia as well as ovarian and colon primary tumors, using Cluster software (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). When all the

samples were included in the hierarchical clustering analysis, the primary colon tumors clustered with the normal colon epithelium, but colon cell lines clustered with the ovarian specimens. Clearly, the tissue clustering that was readily apparent when comparing primary tissues or immortalized lines was lost when including carcinoma cell lines. For example, A2780, a widely used ovarian cancer cell line was just as similar to colon cancer cell lines as it was to ovarian cancer cell lines. This observation supports the idea that in the process of establishment, cell lines may lose many of the gene expression characteristics of their tissue of origin, although tissue specific expression is clearly not completely lost in cancer cell lines (Ross, D. T., et al. *Nat. Genet.* 24:227-235, 2000).

It is widely believed that epithelial ovarian cancer and benign ovarian cysts, while not necessarily part of a progression sequence toward malignancy, are both derived from the ovarian surface epithelium (Scully, R. E. *J. Cell Biochem.* 23, Suppl.:208-218, 1995). OSE cells themselves are mesodermal in origin and are believed to undergo metaplasia before progressing to neoplasia (Scully, R. E. *J. Cell Biochem.* 23 Suppl.:208-218, 1995; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). On the other hand, it has also been argued that ovarian cancers are not derived from OSE but rather from the secondary Mullerian system, structures lined by Mullerian epithelium but located outside the uterus, cervix and fallopian tubes (Schink, J. C. *Semin. Oncol.* 26 Suppl. 1: 2-7, 1999). This hypothesis would explain some of the shortcomings of the OSE model, such as the requirement for metaplasia and the lack of well-defined precursors in the ovary. While not wishing to be bound by theory, our results are consistent with the widely accepted dogma of the OSE origin of ovarian cancer. Indeed, IOSE29 showed high degrees of similarity to the ovarian tumors and both IOSE29 and HOSE were much more closely related to ovarian than colon primary cancers.

E-cadherin expression has been proposed to be a major determinant in the formation of metaplastic OSE (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). Consistent with this hypothesis, E-cadherin was absent in IOSE29, HOSE and ML10 but was expressed in all three ovarian tumors (Table 4). Other cadherins are also shown for comparison. Interestingly, VE-cadherin is absent in

most libraries except in two of the pre-neoplastic ovarian samples, again suggesting metaplasia. As expected, LI-Cadherin was expressed exclusively in the colon-derived libraries. Interestingly, vimentin, a mesenchymal marker, was present in essentially all the ovarian libraries but very low in the colon specimens. Although the specificity of  
5 vimentin as a mesenchymal marker has been questioned, this suggests that OSE may retain some of their mesenchymal characteristics, even after turning on the expression of E-cadherin.

The cytokeratins (CKs) and carcinoembryonic antigen (CEA) have been used to differentiate between colon cancer and ovarian cancer (Lagendijk, J. H., et al. *Hum.*  
10 *Pathol.* 29:491-497, 1998; and Berezowski, K., et al. *Mod. Pathol.* 9:426-429, 1996). Typically, colon cancer expresses CK20 and CEA while ovarian cancer expresses CK7. The expression patterns in our libraries were consistent with previously reported observations: CK20 and CEA were found in normal colon and colon tumors but absent from all of our ovarian samples (Table 4). Conversely, CK7 was expressed in all three  
15 primary ovarian tumors and, while not absent, was much lower in the colon samples. Examination of the differential expression patterns of a variety of established ovarian cancer markers thus provided validation of the SAGE database and cluster analysis.

### Differential gene expression

20 The ultimate goal of comparing SAGE libraries is to identify differentially expressed genes. Criteria for differential expression can be determined for each comparison and transcripts within the determined range selected for study. We found a large number of genes that were up-regulated in only one or two of the three tumors on which SAGE was performed. For example, a total of 444 genes were up-regulated  
25 more than 10-fold in at least one of the three ovarian primary cancers compared to IOSE29. However, only 45 genes were overexpressed more than 10-fold in all three ovarian tumors analyzed compared to IOSE29.

Our analysis of three different primary ovarian cancers allowed us to reduce the number of candidates by looking for consistency between samples. In order to identify  
30 genes that are very likely to be frequently up-regulated during ovarian tumorigenesis we set the following conservative criteria for our analysis. First, the fold induction was calculated by adding the number of normalized tags from the three primary tumors and

dividing this number by the total normalized tags in the three non-malignant specimens. Cell lines were not included here for reasons described above. In addition, although HOSE-4 appeared more distantly related to the other non-transformed specimens, we believe that the inclusion of HOSE-4, while possibly eliminating real candidates makes our analysis more conservative and more likely to identify truly overexpressed genes in ovarian cancer. Second, all three primary tumors were required to consistently show elevated levels ( $>12$  tags/100,000) of the gene in question. This eliminated genes that may be very highly overexpressed in one tumor but not in others. Finally, the candidate genes were required to be expressed in at least one ovarian cell line at a level greater than 3 tags/100,000. This last criterion was used to reduce the possibility of identifying genes because of their high level of expression in inflammatory cells or in the stroma of the primary tumors. Using these criteria, the genes that exhibited more than 10-fold overexpression were identified and are shown in Table 4.

Two members of the Claudin family of tight junction proteins, Claudin-3 and -4 were found among the top six differentially expressed genes and likely represent transmembrane receptors. In addition, Apolipoprotein J (ApoJ) and Apolipoprotein E (ApoE) were both overexpressed in ovarian cancer.

Of the 27 overexpressed genes shown in Table 4, ten were relatively specific for the ovary (HLA-DR, two different ESTs, GA733-1, ceruloplasmin, glutathione peroxidase-3, the secretory leukocyte protease inhibitor, ApoJ, ApoE and mesothelin) while the others were also expressed in colon tissues. In any event, it is significant that MUC1, HE4, Ep-CAM and mesothelin, four genes already known to be up-regulated in epithelial ovarian cancer, were identified in this study. This fact validates our approach as well as our set of criteria used to determine the genes differentially expressed.

Similarly, stringent criteria were used to identify genes down-regulated in ovarian tumors compared to IOSE29, HOSE-4 and ML10. Again, the fold difference was calculated by adding tag frequency for all three "normal" specimens and dividing by the total number of tags in the three ovarian tumors. A candidate was required to be expressed at a level of 12 tags/100,000 or greater in all three normal samples. The genes found elevated more than ten-fold in normal tissue compared to tumors are shown in Table 4.

Table 4. A subset of genes differentially expressed in ovarian tumors compared to non-malignant ovarian samples

SEQ ID NO. (TAG)	TAG	GENE	EXPRESSION					FUNCTION
			Fold	OSE ML10	Ovarian Tumors	Colon Epithelium	Colon Tumors	
103	GGGCAATCTCT	up-regulated <sup>a</sup>	289	-	++	-	-	Major histocompatibility complex, class II/ antigen presentation
104	TTTGGGCCCTA	HLA-DR $\alpha$ chain	123	-	++	+	-	LIM/double zinc finger
105	ATCGTGGCGG	Cysteine-rich protein 1	109	-	+	++	+	Tight junction barrier function
106	TATTATGGTA	Claudin 4	101	-	+	-	-	Unknown
107	GCCTACCCGA	ESTs (HOST-2)	93	-	+	-	-	Tumor Ag/ Ca <sup>2+</sup> signal transducer
108	CTCGCGCTGG	Surface marker 1/ GA733-1/ TROP2	83	-	+	++	+	Tight junction barrier function
109	TTGCTTGCCA	Claudin 3	79	-	+	-	-	Secreted metalloprotein/ antioxidant
110	CCTGCTTGTC	Ceruloplasmin (ferroxidase)	72	-	++	+	-	Secreted protease inhibitor
111	AGGAGGGGC	HE4	69	-	++	-	-	Secreted selenoprotein/ peroxidase
112	CTGTGATCTGC	Glutathione peroxidase 3 (plasma)	60	-	++	-	-	Secreted serine protease inhibitor
113	ACCATTTGGAT	Secretory leukocyte protease inhibitor	56	-	+	-	-	Unknown
114	AGTTTGTGTAG	ESTs (HOST-1)	49	-	++	-	+	Receptor for interferon signaling
115	CCTGGGAATTC	Interferon-induced transmembrane protein 1	48	-	+	++	+	Tumor Ag/ Ca <sup>2+</sup> -independent CAM/ proliferation
116	CAACTAATATC	Ep-CAM/ EGP2/ TROP1/ GA733-2	43	-	++	+	+	Tumor Ag/ Type-I membrane glycoprotein
117	CGACCCACAG	Mucin 1	39	-	++	-	-	Secreted chaperone/ cytoprotection
118	TTCTGTGCTG	Apolipoprotein J/ clusterin	34	-	++	++	+	Transmembrane/ protease inhibitor
119	CGCTGCATGTC	Serine protease inhibitor, Kunitz type, 2	34	-	++	-	-	Lipoprotein particle binding, internalization and catabolism
120	GATCAGGCCA	Apolipoprotein E	24	-	+	-	-	Serine protease of complement system/ autoimmune diseases
121	GTGGAAGACG	Complement component 1, r subcomponent	24	-	++	+	+	Interferon primary response/ $\alpha$ IFN-inducible
122	GATGAGGAGA	GIP3/ IFI-6-16	17	-	++	-	-	Possible cell surface receptor/ immunoglobulin superfamily
123	CCCCCTGCAG	Lutheran blood group protein/ BCAM	16	-	++	-	+	Unknown
124	TGCTGCCTGT	Collagen Type III, alpha-1	16	-	++	-	-	Trans-Golgi membrane protein (epithelial cells)/ T-cell differentiation
124	TGCAGCACGA	Mal (T cell differentiation protein)	13	+	++	-	+	Unknown
126		ESTs (Collagen Type I, alpha-2)	13	-	+	-	-	Major histocompatibility complex, class II/ antigen presentation
127		HLA-DPB1	12	-	++	-	-	GPI-anchored mesothelioma and ovarian cancer antigen/ cell adhesion
128		Mesothelin	12	-	++	-	+	Type II transmembrane protein/ pre-B-cell growth
129		Bone marrow stroma antigen 2/ BST-2	10	-	++	++	+	Major histocompatibility complex, class I/ antigen presentation
129		HLA-Cw	10	-	++	++	+	Major histocompatibility complex, class I/ antigen presentation
130		down-regulated <sup>b</sup>						
130	GGTATTTTGG	Unknown	99	+	-	-	-	Unknown
131	TGTATCATCA	Lysyl oxidase-like 2	73	+	-	-	-	Secreted/ collagen and elastin crosslinker
132	AAAAATAACA	Chloride intracellular channel 4 like	29	+	-	-	-	Ion transport
133	TAAAATGTTT	Plasminogen activator inhibitor, type 1	26	++	-	-	-	Serine protease inhibitor family/ rPA inhibitor
133	GAGCTTTTGA	EST	14	+	-	-	-	Unknown
134	GGCTGATGTG	Glycine t-RNA synthetase	13	+	-	-	-	Protein synthesis
135	CGACGAGGAG	Epithelial membrane protein-3	13	+	-	-	-	Proliferation, differentiation, and apoptosis
136	GCCCCAATA	Galectin-1	10	++	+	-	-	$\beta$ -galactoside binding lectin/ ECM interaction and proliferation
137	GCAACTTGGA	Vinexin $\beta$	10	+	-	-	-	Cell-adhesion and cytoarchitecture
138								

<sup>a</sup> Candidates up-regulated at least 30-fold in tumors<sup>b</sup> Candidates down-regulated at least 10-fold in tumors<sup>c</sup> Expression is defined as: -, 0-9 tags/100,000; +, 10-49 tags/100,000; ++, > 49 tags/100,000

In order to validate the candidates identified by SAGE, we performed immunohistochemical analysis of thirteen cases of serous cancer of the ovary using antibodies against four of the genes identified as up-regulated in ovarian cancer (Table 5). This was particularly important since the SAGE analysis was initially performed from primary ovarian cancers, which contain a mixture of cell types. Ep-CAM exhibited diffuse, strong staining of tumor cell membranes in all thirteen tumors, without blood cell or stromal staining. Importantly, only one of six samples of the ovarian surface epithelium present in the cases showed weak focal staining, and the rest were negative. The strong immunoreactivity of all thirteen ovarian tumors confirms the validity of our approach to identify genes highly and consistently up-regulated in ovarian cancer. Similarly, ApoJ was found to be expressed in ovarian cancer cells and absent from the surface epithelium. While some expression was detected in non-tumor stroma and inflammatory cells, most of the immuno-reactivity was in tumor cells, and a majority (nine out of thirteen) of the cases showed staining. This observation represents the first report of ApoJ expression in ovarian cancer and provides a novel target for diagnosis or therapy. Claudin-3 and -4 also exhibited staining limited to the tumor component of the specimens. Most tumor cells showed strong membrane staining with weak cytoplasmic reactivity. Some tumors specimens showed decreased membrane staining with strong cytoplasmic reactivity. The normal surface epithelial component (or mesothelial cells) examined did not stain or only stained weakly with the Claudin-4 antibody, while the determination of Claudin-3 levels in normal epithelium was complicated by a low background reactivity with this antibody.

#### Incorporation by Reference

Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by reference in their entireties to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

### Other Embodiments

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.



What is claimed is:

1. A method of detecting an ovarian tumor in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in said subject.
2. A method of identifying a subject at increased risk for developing ovarian cancer, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.
3. A method of determining the effectiveness of an ovarian cancer treatment in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject after treatment of said subject, wherein a modulation in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in said subject prior to said treatment, indicates an effective ovarian cancer treatment in said subject.
4. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined in said subject by measuring the expression level of said tumor marker gene in a sample from said subject.

5. The method of claim 4, wherein said sample from said subject is selected from the group consisting of a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, and serum.

6. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is measured *in vivo* in said subject.

7. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is determined by measuring the level of ovarian tumor marker mRNA.

8. The method of claim 7, wherein said level of ovarian tumor marker mRNA is measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization.

9. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined by measuring the level of ovarian tumor marker polypeptide encoded by said ovarian tumor marker gene.

10. The method of claim 9, wherein said level of ovarian tumor marker polypeptide is measured by ELISA, immunoblotting, or immunohistochemistry.

11. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is compared to the expression level of said tumor marker gene in a reference subject diagnosed with ovarian cancer.

12. The method of claim 2, wherein said expression level of said ovarian tumor marker gene in said subject is compared to the expression level of said tumor marker gene in a reference subject that is identified as having an increased risk for developing ovarian cancer.

13. A method of identifying a tumor as an ovarian tumor, said method comprising measuring the expression level of an ovarian tumor marker gene in a tumor cell from said tumor, wherein an increase in said expression level of said ovarian tumor marker gene in said tumor cell, relative to the expression level of said ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

14. A method of treating or preventing an ovarian tumor in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in said subject.

15. A method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in said ovarian tumor cell in said subject.

16. A method of inhibiting the growth or metastasis of an ovarian tumor in a subject, said method comprising contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of said antibody to said ovarian tumor marker polypeptide inhibits the growth or metastasis of said ovarian tumor in said subject.

17. The method of claim 16, wherein said ovarian tumor marker polypeptide is on the surface of said ovarian tumor cell.

18. The method of claim 16, wherein said antibody is coupled to a radioisotope or a toxic compound.

19. A method of diagnosing ovarian cancer in a subject, said method comprising measuring the amount of an ovarian tumor marker polypeptide in said subject, wherein an

amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

20. The method of claim 19, wherein said ovarian tumor marker polypeptide is present at the surface of a cell.

21. The method of claim 19, wherein said ovarian tumor marker polypeptide is in soluble form.

22. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

23. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

24. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

25. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

26. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

27. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

28. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor is an epithelial ovarian tumor.

29. The method of claim 28, wherein said epithelial ovarian tumor is selected from the group consisting of a serous cystadenoma, a borderline serous tumor, a serous cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated carcinoma, a clear cell adenocarcinoma, a cystadenofibroma, an adenofibroma, and a Brenner tumor.

30. A kit comprising an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

31. A kit comprising a nucleic acid for measuring the expression level of an ovarian tumor marker gene in a subject.

32. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

33. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

34. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

35. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

36. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

37. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

## SEQUENCE LISTING

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 Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr  
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 Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro His  
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 Gly Asn Lys Arg His Val Phe His Phe Gly Ala Val Ser Pro Gln Thr  
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 Ser Gln Ala Gly Val Ala Val Met Ala Val Ala Val Ser Val Gly Leu  
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 Leu Leu Leu Val Val Ala Val Phe Tyr Cys Val Arg Arg Lys Gly Gly  
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 Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly Glu  
 580 585 590  
 Pro Gly Leu Ser His Ser Gly Ser Glu Gln Pro Glu Gln Thr Gly Leu  
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 Gly Asp Glu Cys  
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&lt;210&gt; 7

&lt;211&gt; 2780

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 7

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<210> 8  
 <211> 838  
 <212> PRT  
 <213> Homo sapiens

<400> 8

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			20				25						30		
Pro	His	Ala	Met	Arg	Ala	Leu	Trp	Val	Leu	Gly	Leu	Cys	Cys	Val	Leu
		35				40						45			
Leu	Thr	Phe	Gly	Ser	Val	Arg	Ala	Asp	Asp	Glu	Val	Asp	Val	Asp	Gly
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Thr	Val	Glu	Glu	Asp	Leu	Gly	Lys	Ser	Arg	Glu	Gly	Ser	Arg	Thr	Asp
65					70					75				80	
Asp	Glu	Val	Val	Gln	Arg	Glu	Glu	Glu	Ala	Ile	Gln	Leu	Asp	Gly	Leu
				85					90					95	
Asn	Ala	Ser	Gln	Ile	Arg	Glu	Leu	Arg	Glu	Lys	Ser	Glu	Lys	Phe	Ala
			100					105					110		
Phe	Gln	Ala	Glu	Val	Asn	Arg	Met	Met	Lys	Leu	Ile	Ile	Asn	Ser	Leu
		115				120						125			
Tyr	Lys	Asn	Lys	Glu	Ile	Phe	Leu	Arg	Glu	Leu	Ile	Ser	Asn	Ala	Ser
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Leu	Ser	Gly	Asn	Glu	Glu	Leu	Thr	Val	Lys	Ile	Lys	Cys	Asp	Lys	Glu
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Lys	Asn	Leu	Leu	His	Val	Thr	Asp	Thr	Gly	Val	Gly	Met	Thr	Arg	Glu
			180					185					190		
Glu	Leu	Val	Lys	Asn	Leu	Gly	Thr	Ile	Ala	Lys	Ser	Gly	Thr	Ser	Glu
		195				200						205			
Phe	Leu	Asn	Lys	Met	Thr	Glu	Ala	Gln	Glu	Asp	Gly	Gln	Ser	Thr	Ser
	210					215					220				
Glu	Leu	Ile	Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Phe	Leu	Val
225				230						235				240	
Ala	Asp	Lys	Val	Ile	Val	Thr	Ser	Lys	His	Asn	Asn	Asp	Thr	Gln	His
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 Glu Ala Ser Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys  
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 355 360 365  
 Glu Leu Met Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu  
 370 375 380  
 Val Glu Glu Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu  
 385 390 395 400  
 Ser Asp Asp Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val  
 405 410 415  
 Thr Phe Lys Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu  
 420 425 430  
 Phe Asp Glu Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val  
 435 440 445  
 Arg Arg Val Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr  
 450 455 460  
 Leu Asn Phe Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn  
 465 470 475 480  
 Val Ser Arg Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg  
 485 490 495  
 Lys Lys Leu Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp  
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 Leu Gly Val Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu  
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 545 550 555 560  
 Gln Tyr Val Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met  
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 Ala Gly Ser Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg  
 580 585 590  
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 Glu Tyr Cys Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln  
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 Asn Val Ala Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys  
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 Glu Ser Arg Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp  
 645 650 655  
 Met Lys Asp Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser  
 660 665 670  
 Gln Arg Leu Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly  
 675 680 685  
 Trp Ser Gly Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr  
 690 695 700  
 Gly Lys Asp Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe  
 705 710 715 720  
 Glu Ile Asn Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile  
 725 730 735

Lys Glu Asp Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu  
                   740                  745                  750  
 Phe Glu Thr Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys  
                   755                  760                  765  
 Ala Tyr Gly Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile  
                   770                  775                  780  
 Asp Pro Asp Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu  
   785                  790                  795                  800  
 Thr Ala Glu Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu  
                   805                  810                  815  
 Met Asp Val Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr  
                   820                  825                  830  
 Ala Glu Lys Asp Glu Leu  
                   835

&lt;210&gt; 9

&lt;211&gt; 2912

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 9

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&lt;210&gt; 10

&lt;211&gt; 732

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

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20      25      30
Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu
35      40      45
Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Thr Leu
50      55      60
Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu
65      70      75      80
Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile
85      90      95
Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys
100     105     110
Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile
115     120     125
Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val
130     135     140
Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr
145     150     155     160
Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr
165     170     175
Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu
180     185     190
Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys
195     200     205
Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys
210     215     220
Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp
225     230     235     240
Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro
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Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly
260     265     270
Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
275     280     285
Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
290     295     300
Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp
305     310     315     320
Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu
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 Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu  
                   405                  410                  415  
 Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu  
                   420                  425                  430  
 Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly  
                   435                  440                  445  
 Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg  
                   450                  455                  460  
 Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr  
 465                  470                  475                  480  
 Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly  
                   485                  490                  495  
 Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg  
                   500                  505                  510  
 Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr  
                   515                  520                  525  
 Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val  
                   530                  535                  540  
 Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Lys Lys Lys  
 545                  550                  555                  560  
 Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys  
                   565                  570                  575  
 Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu  
                   580                  585                  590  
 Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala  
                   595                  600                  605  
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                   610                  615                  620  
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 Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp  
                   645                  650                  655  
 Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu  
                   660                  665                  670  
 Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile  
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 Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr  
                   690                  695                  700  
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 Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp  
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&lt;210&gt; 11

&lt;211&gt; 2227

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 11

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&lt;210&gt; 12

&lt;211&gt; 573

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

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Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
      20              25              30
Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
      35              40              45
Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
      50              55              60
Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
      65              70              75              80
Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
      85              90              95
Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
      100             105             110
Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
      115             120             125
Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
      130             135             140

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Met	Leu	Ala	Val	Asp	Ala	Val	Ile	Ala	Glu	Leu	Lys	Lys	Gln	Ser	Lys
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Ser	Pro	Tyr	Phe	Ile	Asn	Thr	Ser	Lys	Gly	Gln	Lys	Cys	Glu	Phe	Gln
225					230					235					240
Asp	Ala	Tyr	Val	Leu	Leu	Ser	Glu	Lys	Lys	Ile	Ser	Ser	Ile	Gln	Ser
				245					250					255	
Ile	Val	Pro	Ala	Leu	Glu	Ile	Ala	Asn	Ala	His	Arg	Lys	Pro	Leu	Val
			260					265					270		
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Gly	Gly	Ala	Val	Phe	Gly	Glu	Glu	Gly	Leu	Thr	Leu	Asn	Leu	Glu	Asp
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Val	Gln	Pro	His	Asp	Leu	Gly	Lys	Val	Gly	Glu	Val	Ile	Val	Thr	Lys
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Asp	Asp	Ala	Met	Leu	Leu	Lys	Gly	Lys	Gly	Asp	Lys	Ala	Gln	Ile	Glu
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Lys	Arg	Ile	Gln	Glu	Ile	Ile	Glu	Gln	Leu	Asp	Val	Thr	Thr	Ser	Glu
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Tyr	Glu	Lys	Glu	Lys	Leu	Asn	Glu	Arg	Leu	Ala	Lys	Leu	Ser	Asp	Gly
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Val	Ala	Val	Leu	Lys	Val	Gly	Gly	Thr	Ser	Asp	Val	Glu	Val	Asn	Glu
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Lys	Lys	Asp	Arg	Val	Thr	Asp	Ala	Leu	Asn	Ala	Thr	Arg	Ala	Ala	Val
			420					425					430		
Glu	Glu	Gly	Ile	Val	Leu	Gly	Gly	Cys	Ala	Leu	Leu	Arg	Cys	Ile	
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Ile	Glu	Ile	Ile	Lys	Arg	Thr	Leu	Lys	Ile	Pro	Ala	Met	Thr	Ile	Ala
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Lys	Asn	Ala	Gly	Val	Glu	Gly	Ser	Leu	Ile	Val	Glu	Lys	Ile	Met	Gln
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Ser	Ser	Ser	Glu	Val	Gly	Tyr	Asp	Ala	Met	Ala	Gly	Asp	Phe	Val	Asn
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Met	Val	Glu	Lys	Gly	Ile	Ile	Asp	Pro	Thr	Lys	Val	Val	Arg	Thr	Ala
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<210> 13  
 <211> 2376  
 <212> DNA  
 <213> Homo sapiens

&lt;400&gt; 13

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gccaccgccc cagcgcaaaa cttgggctcg cgcttcccgg cccggcgcgg agcccggggc      300
gcccggagcc ccgccatgtc gcgatccaac cggcagaagg agtacaatg cggggacctg      360
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&lt;210&gt; 14

&lt;211&gt; 240

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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Phe Ala Lys Met Lys Gly Tyr Pro His Trp Pro Ala Arg Ile Asp Glu
 20             25             30
Met Pro Glu Ala Ala Val Lys Ser Thr Ala Asn Lys Tyr Gln Val Phe
 35             40             45
Phe Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe
 50             55             60
Pro Tyr Glu Glu Ser Lys Glu Lys Phe Gly Lys Pro Asn Lys Arg Lys
 65             70             75             80
Gly Phe Ser Glu Gly Leu Trp Glu Ile Glu Asn Asn Pro Thr Val Lys
 85             90             95

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 145 150 155 160  
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 165 170 175  
 Gly Glu Glu Lys Glu Ala Ala Thr Leu Glu Val Glu Arg Pro Leu Pro  
 180 185 190  
 Met Glu Val Glu Lys Asn Ser Thr Pro Ser Glu Pro Gly Ser Gly Arg  
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 <213> Homo sapiens

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&lt;210&gt; 16

&lt;211&gt; 921

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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		20						25					30		
Gln	Glu	Arg	Glu	Leu	Thr	Gln	Leu	Arg	Glu	Lys	Leu	Arg	Glu	Gly	Arg
		35					40					45			
Asp	Ala	Ser	Arg	Ser	Leu	Asn	Glu	His	Leu	Gln	Ala	Leu	Leu	Thr	Pro
		50				55					60				
Asp	Glu	Pro	Asp	Lys	Ser	Gln	Gly	Gln	Asp	Leu	Gln	Glu	Gln	Leu	Ala
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Glu	Gly	Cys	Arg	Leu	Ala	Gln	His	Leu	Val	Gln	Lys	Leu	Ser	Pro	Glu
		85						90						95	
Asn	Asp	Asn	Asp	Asp	Asp	Glu	Asp	Val	Gln	Val	Glu	Val	Ala	Glu	Lys
		100						105					110		
Val	Gln	Lys	Ser	Ser	Ala	Pro	Arg	Glu	Met	Gln	Lys	Ala	Glu	Glu	Lys
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Glu	Val	Pro	Glu	Asp	Ser	Leu	Glu	Glu	Cys	Ala	Ile	Thr	Cys	Ser	Asn
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Asp	Asp	Glu	Glu	Glu	Glu	Glu	Lys	Gly	Pro	Val	Ser	Pro	Arg	Asn	Leu
		195					200					205			



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 740 745 750  
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 755 760 765  
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 770 775 780  
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 Thr Pro Ser Met Tyr Phe Glu Leu Pro Asp Ser Phe Gln His Tyr Arg  
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 915 920

<210> 17  
 <211> 664  
 <212> DNA  
 <213> Homo sapiens

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 gtgcccata gaaccaagcg gcgcctggag gaggagcagg agcctctgcg caagcagttt 180  
 ctgtctgagg agaacatggc caccacttc tctcaactca gcctgcacaa tgaccacccc 240  
 tactgcagcc ccccatgac cttctcccca gccctgcccc cactcaggag cccttgctct 300  
 gagctgcttc tctggcgcta tcctggcagc ctcacccctg aggcctccg tctgctgagg 360  
 ctgggggaca ccccgagtc cccctaccct gcaaccccag ctggggacat aatggagctc 420  
 tgagtgtctg tggacagtgc cctcccacc ttccttcttc ccacaacag aagagaccag 480  
 cgactcccgc aaagggacaa ggttcctccc tctcctgcag agtaggcac tgggcaccaa 540  
 gaccttcct caacagagga cactgagccc aacggagttc tgggatggga ggggtgggag 600  
 catgggaagg gaggcacccc accccaaga agaactgaat aaagattgct gagcaaagga 660  
 aggc 664

<210> 18  
 <211> 138  
 <212> PRT  
 <213> Homo sapiens

<400> 18  
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 Arg Leu Pro Arg Ala Ala Leu Gly Val Thr Trp Gly Leu Asp Ala Ser  
 20 25 30



Ser Pro Leu Arg Gly Ala Val Pro Met Ser Thr Lys Arg Arg Leu Glu  
 35 40 45  
 Glu Glu Gln Glu Pro Leu Arg Lys Gln Phe Leu Ser Glu Glu Asn Met  
 50 55 60  
 Ala Thr His Phe Ser Gln Leu Ser Leu His Asn Asp His Pro Tyr Cys  
 65 70 75 80  
 Ser Pro Pro Met Thr Phe Ser Pro Ala Leu Pro Pro Leu Arg Ser Pro  
 85 90 95  
 Cys Ser Glu Leu Leu Leu Trp Arg Tyr Pro Gly Ser Leu Ile Pro Glu  
 100 105 110  
 Ala Leu Arg Leu Leu Arg Leu Gly Asp Thr Pro Ser Pro Pro Tyr Pro  
 115 120 125  
 Ala Thr Pro Ala Gly Asp Ile Met Glu Leu  
 130 135

<210> 19  
 <211> 2056  
 <212> DNA  
 <213> Homo sapiens

<400> 19  
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 cagagcgtct ggtgagatgc tgttgccgct gctgctgctg ctacccatgt gctgggcccgt 180  
 ggaggtcaag agggcccggg gcgtctccct caccaatcat cacttctacg atgagtccaa 240  
 gcctttcacc tgcctggacg gttcggccac catcccatth gatcaggta acgatgacta 300  
 ttgcgactgc aaagatggct ctgacgagcc aggcacggct gcctgtccta atggcagctt 360  
 ccactgcacc aacactggct ataagccct gtatatcccc tccaaccggg tcaacgatgg 420  
 tgtttgtgac tgctgcgatg gaacagacga gtacaacagc ggcgatcatct gtgagaacac 480  
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 cgaagggttc cgtctgaaga agatccttat tgaggactgg aagaaggcac gggaggagaa 600  
 gcagaaaaag ctcatgagc tacaggctgg gaagaagtct ctggaagacc aggtggagat 660  
 gctgcggaca gtgaaggagg aagctgagaa gccagagaga gaggccaaag agcagcacca 720  
 gaagctgtgg gaagagcagc tggctgctgc caaggcccaa caggagcagg agctggcggc 780  
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 catcaggggac aagtaaccgt ccgaggcact gccaccgac cttccagcac cttctgcccc 1020  
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 ggaggcccca ccgccactgt caccgccgca gccggccagc cctgctgagg aagacaaaat 1200  
 gccgcccctac gacgagcaga cgcaggcctt catcgatgct gcccaggagg cccgcaacaa 1260  
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 cgagctcacc accaacgaat acgtctaccg cctctgcccc ttcaagcttg tctcgagaa 1440  
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 ccacgacaag ttcagtgcc tgaagtatga gcaaggcagc ggctgctggc agggccccc 1560  
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 cctgccccc ctccagtgg ggactagtga atgacttgac ctgtgacctc aatacaataa 2040  
 atgtgatccc ccacccc 2056

<210> 20  
 <211> 527  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 20

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Met Leu Leu Pro Leu Leu Leu Leu Leu Pro Met Cys Trp Ala Val Glu
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Val Lys Arg Pro Arg Gly Val Ser Leu Thr Asn His His Phe Tyr Asp
20      25      30
Glu Ser Lys Pro Phe Thr Cys Leu Asp Gly Ser Ala Thr Ile Pro Phe
35      40      45
Asp Gln Val Asn Asp Asp Tyr Cys Asp Cys Lys Asp Gly Ser Asp Glu
50      55      60
Pro Gly Thr Ala Ala Cys Pro Asn Gly Ser Phe His Cys Thr Asn Thr
65      70      75      80
Gly Tyr Lys Pro Leu Tyr Ile Pro Ser Asn Arg Val Asn Asp Gly Val
85      90      95
Cys Asp Cys Cys Asp Gly Thr Asp Glu Tyr Asn Ser Gly Val Ile Cys
100     105     110
Glu Asn Thr Cys Lys Glu Lys Gly Arg Lys Glu Arg Glu Ser Leu Gln
115     120     125
Gln Met Ala Glu Val Thr Arg Glu Gly Phe Arg Leu Lys Lys Ile Leu
130     135     140
Ile Glu Asp Trp Lys Lys Ala Arg Glu Glu Lys Gln Lys Lys Leu Ile
145     150     155     160
Glu Leu Gln Ala Gly Lys Lys Ser Leu Glu Asp Gln Val Glu Met Leu
165     170     175
Arg Thr Val Lys Glu Glu Ala Glu Lys Pro Glu Arg Glu Ala Lys Glu
180     185     190
Gln His Gln Lys Leu Trp Glu Glu Gln Leu Ala Ala Ala Lys Ala Gln
195     200     205
Gln Glu Gln Glu Leu Ala Ala Asp Ala Phe Lys Glu Leu Asp Asp Asp
210     215     220
Met Asp Gly Thr Val Ser Val Thr Glu Leu Gln Thr His Pro Glu Leu
225     230     235     240
Asp Thr Asp Gly Asp Gly Ala Leu Ser Glu Ala Glu Ala Gln Ala Leu
245     250     255
Leu Ser Gly Asp Thr Gln Thr Asp Ala Thr Ser Phe Tyr Asp Arg Val
260     265     270
Trp Ala Ala Ile Arg Asp Lys Tyr Arg Ser Glu Ala Leu Pro Thr Asp
275     280     285
Leu Pro Ala Pro Ser Ala Pro Asp Leu Thr Glu Pro Lys Glu Glu Gln
290     295     300
Pro Pro Val Pro Ser Ser Pro Thr Glu Glu Glu Glu Glu Glu Glu
305     310     315     320
Glu Glu Glu Glu Ala Glu Glu Glu Glu Glu Glu Asp Ser Glu Glu
325     330     335
Ala Pro Pro Pro Leu Ser Pro Pro Gln Pro Ala Ser Pro Ala Glu Glu
340     345     350
Asp Lys Met Pro Pro Tyr Asp Glu Gln Thr Gln Ala Phe Ile Asp Ala
355     360     365
Ala Gln Glu Ala Arg Asn Lys Phe Glu Glu Ala Glu Arg Ser Leu Lys
370     375     380
Asp Met Glu Glu Ser Ile Arg Asn Leu Glu Gln Glu Ile Ser Phe Asp
385     390     395     400
Phe Gly Pro Asn Gly Glu Phe Ala Tyr Leu Tyr Ser Gln Cys Tyr Glu
405     410     415
Leu Thr Thr Asn Glu Tyr Val Tyr Arg Leu Cys Pro Phe Lys Leu Val
420     425     430
Ser Gln Lys Pro Lys Leu Gly Gly Ser Pro Thr Ser Leu Gly Thr Trp
435     440     445
Gly Ser Trp Ile Gly Pro Asp His Asp Lys Phe Ser Ala Met Lys Tyr

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450	455	460
Glu Gln Gly Thr Gly Cys Trp Gln Gly Pro Asn Arg Ser Thr Thr Val		
465	470	475
Arg Leu Leu Cys Gly Lys Glu Thr Met Val Thr Ser Thr Thr Glu Pro		480
	485	490
Ser Arg Cys Glu Tyr Leu Met Glu Leu Met Thr Pro Ala Ala Cys Pro		495
	500	505
Glu Pro Pro Pro Glu Ala Pro Thr Glu Asp Asp His Asp Glu Leu		510
	515	520
		525

<210> 21  
 <211> 384  
 <212> DNA  
 <213> Homo sapiens

<400> 21  
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 aagacaggtg agacttcgag agccctgtca tcttctaaac agagcagcag cagcagagat 180  
 gataacatgt ttcagattgg gaaaatgagg tacgttagtg ttcgcgattt taaaggcaaa 240  
 gtgctaattg atattagaga atattggatg gatcctgaag gtgaaatgaa accaggaaga 300  
 aaaggtattt ctttaaattcc agaacaatgg agccagctga aggaacagat ctctgatata 360  
 gatgacgcag taagaaagct gtga 384

<210> 22  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<400> 22  
 Met Pro Lys Ser Lys Glu Leu Val Ser Ser Ser Ser Ser Gly Ser Asp  
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 Ser Asp Ser Glu Val Asp Lys Lys Leu Lys Arg Lys Lys Gln Val Ala  
 20 25 30  
 Pro Glu Lys Pro Val Lys Lys Gln Lys Thr Gly Glu Thr Ser Arg Ala  
 35 40 45  
 Leu Ser Ser Ser Lys Gln Ser Ser Ser Arg Asp Asp Asn Met Phe  
 50 55 60  
 Gln Ile Gly Lys Met Arg Tyr Val Ser Val Arg Asp Phe Lys Gly Lys  
 65 70 75 80  
 Val Leu Ile Asp Ile Arg Glu Tyr Trp Met Asp Pro Glu Gly Glu Met  
 85 90 95  
 Lys Pro Gly Arg Lys Gly Ile Ser Leu Asn Pro Glu Gln Trp Ser Gln  
 100 105 110  
 Leu Lys Glu Gln Ile Ser Asp Ile Asp Asp Ala Val Arg Lys Leu  
 115 120 125

<210> 23  
 <211> 1554  
 <212> DNA  
 <213> Homo sapiens

<400> 23  
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 cttgtgccgc ggcctggccg tggaggccaa gaagacttac gtgcgcgaca agccacatgt 180  
 gaatgtgggt accatcgccc atgtggacca cggaagacc acgctgactg cagccatcac 240  
 gaagattcta gctgagggag gtggggctaa gttcaagaag tacgaggaga ttgacaatgc 300  
 cccggaggag cgagctcggg gtatcaccat caatgcggct catgtggagt atagcactgc 360  
 cgcccgccac tacgccaca cagactgccc gggatcatgca gattatgtta agaatatgat 420

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gtatgtgaac aaggctgacg ctgtccagga ctctgagatg gtggaactgg tggaactgga 600
gateccgggag ctgctcaccg agtttggtta taaaggggag gagaccccag tcatcgtagg 660
ctctgctctc tgtgcccttg agggtcggga ccctgagtta ggcctgaagt ctgtgcagaa 720
gctactggat gctgtggaca cttacatccc agtgcccgcc cgggacctgg agaagccttt 780
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ggaagggttg gcctgcctgg ctggggaggt cagtaaactt tgaatagtaa gcca 1554

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&lt;210&gt; 24

&lt;211&gt; 452

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

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Met Ala Ala Ala Thr Leu Leu Arg Ala Thr Pro His Phe Ser Gly Leu
1      5      10      15
Ala Ala Gly Arg Thr Phe Leu Leu Gln Gly Leu Leu Arg Leu Leu Lys
20      25      30
Ala Pro Ala Leu Pro Leu Leu Cys Arg Gly Leu Ala Val Glu Ala Lys
35      40      45
Lys Thr Tyr Val Arg Asp Lys Pro His Val Asn Val Gly Thr Ile Gly
50      55      60
His Val Asp His Gly Lys Thr Thr Leu Thr Ala Ala Ile Thr Lys Ile
65      70      75      80
Leu Ala Glu Gly Gly Gly Ala Lys Phe Lys Lys Tyr Glu Glu Ile Asp
85      90      95
Asn Ala Pro Glu Glu Arg Ala Arg Gly Ile Thr Ile Asn Ala Ala His
100     105     110
Val Glu Tyr Ser Thr Ala Ala Arg His Tyr Ala His Thr Asp Cys Pro
115     120     125
Gly His Ala Asp Tyr Val Lys Asn Met Ile Thr Gly Thr Ala Pro Leu
130     135     140
Asp Gly Cys Ile Leu Val Val Ala Ala Asn Asp Gly Pro Met Pro Gln
145     150     155     160
Thr Arg Glu His Leu Leu Leu Ala Arg Gln Ile Gly Val Glu His Val
165     170     175
Val Val Tyr Val Asn Lys Ala Asp Ala Val Gln Asp Ser Glu Met Val
180     185     190
Glu Leu Val Glu Leu Glu Ile Arg Glu Leu Leu Thr Glu Phe Gly Tyr
195     200     205
Lys Gly Glu Glu Thr Pro Val Ile Val Gly Ser Ala Leu Cys Ala Leu
210     215     220
Glu Gly Arg Asp Pro Glu Leu Gly Leu Lys Ser Val Gln Lys Leu Leu
225     230     235     240
Asp Ala Val Asp Thr Tyr Ile Pro Val Pro Ala Arg Asp Leu Glu Lys
245     250     255
Pro Phe Leu Leu Pro Val Glu Ala Val Tyr Ser Val Pro Gly Arg Gly
260     265     270

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Thr Val Val Thr Gly Thr Leu Glu Arg Gly Ile Leu Lys Lys Gly Asp  
 275 280 285  
 Glu Cys Glu Leu Leu Gly His Ser Lys Asn Ile Arg Thr Val Val Thr  
 290 295 300  
 Gly Ile Glu Met Phe His Lys Ser Leu Glu Arg Ala Glu Ala Gly Asp  
 305 310 315 320  
 Asn Leu Gly Ala Leu Val Arg Gly Leu Lys Arg Glu Asp Leu Arg Arg  
 325 330 335  
 Gly Leu Val Met Val Lys Pro Gly Ser Ile Lys Pro His Gln Lys Val  
 340 345 350  
 Glu Ala Gln Val Tyr Ile Leu Ser Lys Glu Glu Gly Gly Arg His Lys  
 355 360 365  
 Pro Phe Val Ser His Phe Met Pro Val Met Phe Ser Leu Thr Trp Asn  
 370 375 380  
 Met Ala Cys Arg Ile Ile Leu Pro Pro Glu Lys Glu Leu Ala Met Pro  
 385 390 395 400  
 Gly Glu Asp Leu Lys Phe Asn Leu Ile Leu Arg Gln Pro Met Ile Leu  
 405 410 415  
 Glu Lys Gly Gln Arg Phe Thr Leu Arg Asp Gly Asn Arg Thr Ile Gly  
 420 425 430  
 Thr Gly Leu Val Thr Asn Thr Leu Ala Met Thr Glu Glu Glu Lys Asn  
 435 440 445  
 Ile Lys Trp Gly  
 450

<210> 25  
 <211> 2201  
 <212> DNA  
 <213> Homo sapiens

<400> 25  
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 ggcttgccct ggtcttgctc ggccgatgaa gtgcagagggt ttttttctga ctgcaaaatt 180  
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 gggcacagggt atattgaaat ctttaagagc agtagagctg aagttagaac tcattatgat 660  
 ccaccacgaa agcttatggc catgcagcgg ccaggtcctt atgacagacc tggggctggt 720  
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 tcagatagat ttggaagaga cctcaattac tgtttttcag gaatgtctga tcacagatac 900  
 ggggatgggt gctctacttt ccagagcaca acaggacact gtgtacacat gcggggatta 960  
 ccttacagag ctactgagaa tgacatttat aatttttttt caccgctcaa ccctgtgaga 1020  
 gtacacattg aaattggtcc tgatggcaga gtaactgggtg aagcagatgt cgagttcgca 1080  
 actcatgaag atgctgtggc agctatgtca aaagacaaaag caaatatgca acacagatat 1140  
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 gtagaactct tcttgaattc tacagcagga gcaagcgggtg gtgcttatgg tagccaaatg 1260  
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 gactcttggt caaccttttt tttttttttt ttttctttaa gaaaacttca gtttaacagt 1620  
 ttctgcaata caagcttggt atttatgctt actctaagtg gaaatcagga ttgttatgaa 1680  
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taaaactataa ctgttaaact taagttccag cttttctcaa gttagttata ggatgtactt 1800
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gttaaaattga acactgtttt ggatgcatgt tgaaagacat gcttttattt tttttgtaaa 1920
acaatatagg agctgtgtct actattaaaa gtgaaacatt ttggcatgtt tgtaattctt 1980
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ttctgaggcc ttgatttaaa tctttcattg tattgtgatt tccttttagg tatattgcgc 2160
taagtgaaac ttgtcaaata aatcctcctt ttaaaaactg c 2201

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&lt;210&gt; 26

&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 26

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Met Met Leu Gly Thr Glu Gly Gly Glu Gly Phe Val Val Lys Val Arg
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Gly Leu Pro Trp Ser Cys Ser Ala Asp Glu Val Gln Arg Phe Phe Ser
20     25     30
Asp Cys Lys Ile Gln Asn Gly Ala Gln Gly Ile Arg Phe Ile Tyr Thr
35     40     45
Arg Glu Gly Arg Pro Ser Gly Glu Ala Phe Val Glu Leu Glu Ser Glu
50     55     60
Asp Glu Val Lys Leu Ala Leu Lys Lys Asp Arg Glu Thr Met Gly His
65     70     75     80
Arg Tyr Val Glu Val Phe Lys Ser Asn Asn Val Glu Met Asp Trp Val
85     90     95
Leu Lys His Thr Gly Pro Asn Ser Pro Asp Thr Ala Asn Asp Gly Phe
100    105    110
Val Arg Leu Arg Gly Leu Pro Phe Gly Cys Ser Lys Glu Glu Ile Val
115    120    125
Gln Phe Phe Ser Gly Leu Glu Ile Val Pro Asn Gly Ile Thr Leu Pro
130    135    140
Val Asp Phe Gln Gly Arg Ser Thr Gly Glu Ala Phe Val Gln Phe Ala
145    150    155    160
Ser Gln Glu Ile Ala Glu Lys Ala Leu Lys Lys His Lys Glu Arg Ile
165    170    175
Gly His Arg Tyr Ile Glu Ile Phe Lys Ser Ser Arg Ala Glu Val Arg
180    185    190
Thr His Tyr Asp Pro Pro Arg Lys Leu Met Ala Met Gln Arg Pro Gly
195    200    205
Pro Tyr Asp Arg Pro Gly Ala Gly Arg Gly Tyr Asn Ser Ile Gly Arg
210    215    220
Gly Ala Gly Phe Glu Arg Met Arg Arg Gly Ala Tyr Gly Gly Gly Tyr
225    230    235    240
Gly Gly Tyr Asp Asp Tyr Asn Gly Tyr Asn Asp Gly Tyr Gly Phe Gly
245    250    255
Ser Asp Arg Phe Gly Arg Asp Leu Asn Tyr Cys Phe Ser Gly Met Ser
260    265    270
Asp His Arg Tyr Gly Asp Gly Gly Ser Thr Phe Gln Ser Thr Thr Gly
275    280    285
His Cys Val His Met Arg Gly Leu Pro Tyr Arg Ala Thr Glu Asn Asp
290    295    300
Ile Tyr Asn Phe Phe Ser Pro Leu Asn Pro Val Arg Val His Ile Glu
305    310    315    320
Ile Gly Pro Asp Gly Arg Val Thr Gly Glu Ala Asp Val Glu Phe Ala
325    330    335
Thr His Glu Asp Ala Val Ala Ala Met Ser Lys Asp Lys Ala Asn Met
340    345    350

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Gln His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr Ala Gly Ala Ser  
                   355                                  360                                  365  
 Gly Gly Ala Tyr Glu His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr  
                   370                                  375                                  380  
 Ala Gly Ala Ser Gly Gly Ala Tyr Gly Ser Gln Met Met Gly Gly Met  
 385                                  390                                  395                                  400  
 Gly Leu Ser Asn Gln Ser Ser Tyr Gly Gly Pro Ala Ser Gln Gln Leu  
                                   405                                  410                                  415  
 Ser Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Gln Ser Ser Met Ser Gly  
                                   420                                  425                                  430  
 Tyr Asp Gln Val Leu Gln Glu Asn Ser Ser Asp Phe Gln Ser Asn Ile  
                   435                                  440                                  445  
 Ala

<210> 27  
 <211> 1852  
 <212> DNA  
 <213> Homo sapiens

<400> 27  
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 ctgagcatca tcttcatccc ggccctgctg cagtgcacg tgctgccctt ctgccccgag 180  
 agtccccgct tcttgetcat caaccgcaac gaggagaacc gggccaagag tgtgctaaag 240  
 aagctgcgcg ggacagctga cgtgacccat gacctgcagg agatgaagga agagagtcgg 300  
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 <211> 343  
 <212> PRT  
 <213> Homo sapiens

<400> 28

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 Asn Lys Asp Leu Trp Pro Leu Leu Ser Ile Ile Phe Ile Pro Ala  
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 Lys Leu Arg Gly Thr Ala Asp Val Thr His Asp Leu Gln Glu Met Lys  
 85 90 95  
 Glu Glu Ser Arg Gln Met Met Arg Glu Lys Lys Val Thr Ile Leu Glu  
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 Leu Gln Leu Ser Gln Gln Leu Ser Gly Ile Asn Ala Val Phe Tyr Tyr  
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 Leu Glu Gln Leu Pro Trp Met Ser Tyr Leu Ser Ile Val Ala Ile Phe  
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&lt;210&gt; 29

&lt;211&gt; 5368

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

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&lt;210&gt; 30

&lt;211&gt; 1338

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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Gly Gln Ala Asp Ala Glu Arg Arg Gln Asp Ile Val Leu Ser Gly Ala
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Gln Arg Leu Asp Tyr Glu Ser Lys Leu Gln Ala Leu Gln Lys Gln Val
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Leu	Lys	Lys	Lys	Val	Gln	Phe	Gln	Phe	Val	Leu	Leu	Thr	Asp	Thr	Leu	
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Tyr	Ser	Pro	Leu	Pro	Pro	Glu	Leu	Leu	Pro	Thr	Glu	Met	Glu	Lys	Thr	
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His	Glu	Asp	Arg	Pro	Phe	Pro	Arg	Thr	Val	Val	Ala	Val	Glu	Val	Gln	
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Pro	Phe	Tyr	Asp	Arg	Phe	His	Trp	Phe	Lys	Leu	Val	Gly	Ser	Ser	Pro	
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 Pro Cys Arg Arg Phe Phe Pro Pro Pro Met Pro Leu Ser Lys Pro Val  
 740 745 750  
 Pro Ala Thr Lys Leu Asn Thr Met Ser Lys Thr Ser Leu Gly Gln Ser  
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 Met Ser Lys Tyr Asp Leu Leu Val Trp Phe Glu Ile Ser Glu Leu Glu  
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 Asp Gln Lys Thr Pro Glu Ala Asn Ser Arg Ala Ser Ser Pro Cys Pro  
 1170 1175 1180  
 Glu Phe Glu Gln Phe Gln Ile Val Pro Ala Val Glu Thr Pro Tyr Leu  
 1185 1190 1195 1200

Ala Arg Ala Gly Lys Asn Glu Phe Leu Asn Leu Val Pro Asp Ile Glu  
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 Glu Ile Arg Pro Ser Ser Val Val Ser Lys Lys Gly Tyr Leu His Phe  
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 Lys Glu Pro Leu Tyr Ser Asn Trp Ala Lys His Phe Val Val Val Arg  
 1235 1240 1245  
 Arg Pro Tyr Val Phe Ile Tyr Asn Ser Asp Lys Asp Pro Val Glu Arg  
 1250 1255 1260  
 Gly Ile Ile Asn Leu Ser Thr Ala Gln Val Glu Tyr Ser Glu Asp Gln  
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 Gln Ala Met Val Lys Thr Pro Asn Thr Phe Ala Val Cys Thr Lys His  
 1285 1290 1295  
 Arg Gly Val Leu Leu Gln Ala Leu Asn Asp Lys Asp Met Asn Asp Trp  
 1300 1305 1310  
 Leu Tyr Ala Phe Asn Pro Leu Leu Ala Gly Thr Ile Arg Ser Lys Leu  
 1315 1320 1325  
 Ser Arg Arg Cys Pro Ser Gln Ser Lys Tyr  
 1330 1335

<210> 31  
 <211> 3094  
 <212> DNA  
 <213> Homo sapiens

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caggaggtgg aggttgcagt gagctgagat cgcgccattg cactcccgcc tgggcgactc 3060
catctctaaa aaaaaaaaaa aaaaaaaaaa aaaa 3094

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&lt;210&gt; 32

&lt;211&gt; 280

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

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Met Cys Ser Ala Phe His Arg Ala Glu Ser Gly Thr Glu Leu Leu Ala
 1          5          10          15
Arg Leu Glu Gly Arg Ser Ser Leu Lys Glu Ile Glu Pro Asn Leu Phe
 20          25          30
Ala Asp Glu Asp Ser Pro Val His Gly Asp Ile Leu Glu Phe His Gly
 35          40          45
Pro Glu Gly Thr Gly Lys Thr Glu Met Leu Tyr His Leu Thr Ala Arg
 50          55          60
Cys Ile Leu Pro Lys Ser Glu Gly Gly Leu Glu Val Glu Val Leu Phe
 65          70          75          80
Ile Asp Thr Asp Tyr His Phe Asp Met Leu Arg Leu Val Thr Ile Leu
 85          90          95
Glu His Arg Leu Ser Gln Ser Ser Glu Glu Ile Ile Lys Tyr Cys Leu
100          105          110
Gly Arg Phe Phe Leu Val Tyr Cys Ser Ser Ser Thr His Leu Leu Leu
115          120          125
Thr Leu Tyr Ser Leu Glu Ser Met Phe Cys Ser His Pro Ser Leu Cys
130          135          140
Leu Leu Ile Leu Asp Ser Leu Ser Ala Phe Tyr Trp Ile Asp Arg Val
145          150          155          160
Asn Gly Gly Glu Ser Val Asn Leu Gln Glu Ser Thr Leu Arg Lys Cys
165          170          175
Ser Gln Cys Leu Glu Lys Leu Val Asn Asp Tyr Arg Leu Val Leu Phe
180          185          190
Ala Thr Thr Gln Thr Ile Met Gln Lys Ala Ser Ser Ser Ser Glu Glu
195          200          205
Pro Ser His Ala Ser Arg Arg Leu Cys Asp Val Asp Ile Asp Tyr Arg
210          215          220
Pro Tyr Leu Cys Lys Ala Trp Gln Gln Leu Val Lys His Arg Met Phe
225          230          235          240
Phe Ser Lys Gln Asp Ser Gln Ser Ser Asn Gln Phe Ser Leu Val
245          250          255
Ser Arg Cys Leu Lys Ser Asn Ser Leu Lys Lys His Phe Phe Ile Ile
260          265          270
Gly Glu Ser Gly Val Glu Phe Cys
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<210> 33  
 <211> 691  
 <212> DNA  
 <213> Homo sapiens

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 agttgttggc cgaagaggcc gtgacgctgg acatgttggc cctgggggca gccaaggcaa 480  
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<210> 34  
 <211> 168  
 <212> PRT  
 <213> Homo sapiens

<400> 34  
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 35 40 45  
 Phe Phe Asn Gly Ala Asn Val Arg Gln Val Asp Val Pro Thr Leu Thr  
 50 55 60  
 Gly Ala Phe Gly Ile Leu Ala Ala His Val Pro Thr Leu Gln Val Leu  
 65 70 75 80  
 Arg Pro Gly Leu Val Val Val His Ala Glu Asp Gly Thr Thr Ser Lys  
 85 90 95  
 Tyr Phe Val Ser Ser Gly Ser Ile Ala Val Asn Ala Asp Ser Ser Val  
 100 105 110  
 Gln Leu Leu Ala Glu Glu Ala Val Thr Leu Asp Met Leu Asp Leu Gly  
 115 120 125  
 Ala Ala Lys Ala Asn Leu Glu Lys Ala Gln Ala Glu Leu Val Gly Thr  
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<210> 35  
 <211> 1378  
 <212> DNA  
 <213> Homo sapiens

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aattacagtg	acttggatca	atcaaagtgt	actgaggaaa	cacctgaagg	tgaagaacat	840
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&lt;210&gt; 36

&lt;211&gt; 2896

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 36

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&lt;210&gt; 37

&lt;211&gt; 777

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 37

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Asp	Leu	Ile	Arg	Gln	Gly	Asp	Thr	Gln	Ala	Lys	Tyr	Ala	Val	Asn	Ser	
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Ile	Lys	Lys	Lys	Val	Asn	Asp	Lys	Asn	Pro	His	Val	Ala	Leu	Tyr	Ala	
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Leu	Glu	Val	Met	Glu	Ser	Val	Val	Lys	Asn	Cys	Gly	Gln	Thr	Val	His	
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Asp	Glu	Val	Ala	Asn	Lys	Gln	Thr	Met	Glu	Glu	Leu	Lys	Asp	Leu	Leu	
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Lys	Arg	Gln	Val	Glu	Val	Asn	Val	Arg	Asn	Lys	Ile	Leu	Tyr	Leu	Ile	
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Gln	Ala	Trp	Ala	His	Ala	Phe	Arg	Asn	Glu	Pro	Lys	Tyr	Lys	Val	Val	
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Phe	Lys	Glu	Ser	Asp	Ala	Met	Phe	Ala	Ala	Glu	Arg	Ala	Pro	Asp	Trp	
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Val	Asp	Ala	Glu	Glu	Cys	His	Arg	Cys	Arg	Val	Gln	Phe	Gly	Val	Met	
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Thr	Arg	Lys	His	His	Cys	Arg	Ala	Cys	Gly	Gln	Ile	Phe	Cys	Gly	Lys	
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Cys	Ser	Ser	Lys	Tyr	Ser	Thr	Ile	Pro	Lys	Phe	Gly	Ile	Glu	Lys	Glu	
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Val	Arg	Val	Cys	Glu	Pro	Cys	Tyr	Glu	Gln	Leu	Asn	Arg	Lys	Ala	Glu	
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Glu	Ala	Glu	Glu	Lys	Glu	Arg	Leu	Arg	Gln	Lys	Ser	Thr	Tyr	Thr	Ser	
	275					280						285				
Tyr	Pro	Lys	Ala	Glu	Pro	Met	Pro	Ser	Ala	Ser	Ser	Ala	Pro	Pro	Ala	
	290					295				300						
Ser	Ser	Leu	Tyr	Ser	Ser	Pro	Val	Asn	Ser	Ser	Ala	Pro	Leu	Ala	Glu	
	305				310				315						320	

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 325 330 335  
 Lys Lys Gln Glu Glu Ala Arg Lys Ser Pro Thr Pro Ser Ala Pro Val  
 340 345 350  
 Pro Leu Thr Glu Pro Ala Ala Gln Pro Gly Glu Gly His Ala Ala Pro  
 355 360 365  
 Thr Asn Val Val Glu Asn Pro Leu Pro Glu Thr Asp Ser Gln Pro Ile  
 370 375 380  
 Pro Pro Ser Gly Gly Pro Phe Ser Glu Pro Gln Phe His Asn Gly Glu  
 385 390 395 400  
 Ser Glu Glu Ser His Glu Gln Phe Leu Lys Ala Leu Gln Asn Ala Val  
 405 410 415  
 Thr Thr Phe Val Asn Arg Met Lys Ser Asn His Met Arg Gly Arg Ser  
 420 425 430  
 Ile Thr Asn Asp Ser Ala Val Leu Ser Leu Phe Gln Ser Ile Asn Gly  
 435 440 445  
 Met His Pro Gln Leu Leu Glu Leu Leu Asn Gln Leu Asp Glu Arg Arg  
 450 455 460  
 Leu Tyr Tyr Glu Gly Leu Gln Asp Lys Leu Ala Gln Ile Arg Asp Ala  
 465 470 475 480  
 Arg Gly Ala Leu Ser Ala Leu Arg Glu Glu His Arg Glu Lys Leu Arg  
 485 490 495  
 Arg Ala Ala Glu Glu Ala Glu Arg Gln Arg Gln Ile Gln Leu Ala Gln  
 500 505 510  
 Lys Leu Glu Ile Met Arg Gln Lys Lys Gln Glu Tyr Leu Glu Val Gln  
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 Arg Gln Leu Ala Ile Gln Arg Leu Gln Glu Gln Glu Lys Glu Arg Gln  
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 Pro Ala Phe Pro Leu Pro Tyr Ala Gln Leu Gln Ala Met Pro Ala Ala  
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 Gly Gly Val Leu Tyr Gln Pro Ser Gly Pro Ala Ser Phe Pro Ser Thr  
 580 585 590  
 Phe Ser Pro Ala Gly Ser Val Glu Gly Ser Pro Met His Gly Val Tyr  
 595 600 605  
 Met Ser Gln Pro Ala Pro Ala Ala Gly Pro Tyr Pro Ser Met Pro Ser  
 610 615 620  
 Thr Ala Ala Asp Pro Ser Met Val Ser Ala Tyr Met Tyr Pro Ala Gly  
 625 630 635 640  
 Ala Thr Gly Ala Gln Ala Ala Pro Gln Ala Gln Ala Gly Pro Thr Ala  
 645 650 655  
 Ser Pro Ala Tyr Ser Ser Tyr Gln Pro Thr Pro Thr Ala Gly Tyr Gln  
 660 665 670  
 Asn Val Ala Ser Gln Ala Pro Gln Ser Leu Pro Ala Ile Ser Gln Pro  
 675 680 685  
 Pro Gln Ser Ser Thr Met Gly Tyr Met Gly Ser Gln Ser Val Ser Met  
 690 695 700  
 Gly Tyr Gln Pro Tyr Asn Met Gln Asn Leu Met Thr Thr Leu Pro Ser  
 705 710 715 720  
 Gln Asp Ala Ser Leu Pro Pro Gln Gln Pro Tyr Ile Ala Gly Gln Gln  
 725 730 735  
 Pro Met Tyr Gln Gln Met Ala Pro Ser Gly Gly Pro Pro Gln Gln Gln  
 740 745 750  
 Pro Pro Val Ala Gln Gln Pro Gln Ala Gln Gly Pro Pro Ala Gln Gly  
 755 760 765  
 Ser Glu Ala Gln Leu Ile Ser Phe Asp  
 770 775

&lt;211&gt; 2569

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

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&lt;210&gt; 39

&lt;211&gt; 478

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

Met	Ala	Gly	Val	Glu	Glu	Val	Ala	Ala	Ser	Gly	Ser	His	Leu	Asn	Gly
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Asp	Leu	Asp	Pro	Asp	Asp	Arg	Glu	Glu	Gly	Ala	Ala	Ser	Thr	Ala	Glu
			20					25						30	

Glu Ala Ala Lys Lys Lys Arg Arg Lys Lys Lys Lys Ser Lys Gly Pro  
           35                                  40                                  45  
 Ser Ala Ala Gly Glu Gln Glu Pro Asp Lys Glu Ser Gly Ala Ser Val  
           50                                  55                                  60  
 Asp Glu Val Ala Arg Gln Leu Glu Arg Ser Ala Leu Glu Asp Lys Glu  
 65                                  70                                  75                                  80  
 Arg Asp Glu Asp Asp Glu Asp Gly Asp Gly Asp Gly Ala Thr  
                                   85                                  90                                  95  
 Gly Lys Lys Lys Lys Lys Lys Lys Lys Arg Gly Pro Lys Val Gln  
                                   100                                  105                                  110  
 Thr Asp Pro Pro Ser Val Pro Ile Cys Asp Leu Tyr Pro Asn Gly Val  
                                   115                                  120                                  125  
 Phe Pro Lys Gly Gln Glu Cys Glu Tyr Pro Pro Thr Gln Asp Gly Arg  
                                   130                                  135                                  140  
 Thr Ala Ala Trp Arg Thr Thr Ser Glu Glu Lys Lys Ala Leu Asp Gln  
 145                                  150                                  155                                  160  
 Ala Ser Glu Glu Ile Trp Asn Asp Phe Arg Glu Ala Ala Glu Ala His  
                                   165                                  170                                  175  
 Arg Gln Val Arg Lys Tyr Val Met Ser Trp Ile Lys Pro Gly Met Thr  
                                   180                                  185                                  190  
 Met Ile Glu Ile Cys Glu Lys Leu Glu Asp Cys Ser Arg Lys Leu Ile  
                                   195                                  200                                  205  
 Lys Glu Asn Gly Leu Asn Ala Gly Leu Ala Phe Pro Thr Gly Cys Ser  
                                   210                                  215                                  220  
 Leu Asn Asn Cys Ala Ala His Tyr Thr Pro Asn Ala Gly Asp Thr Thr  
 225                                  230                                  235                                  240  
 Val Leu Gln Tyr Asp Asp Ile Cys Lys Ile Asp Phe Gly Thr His Ile  
                                   245                                  250                                  255  
 Ser Gly Arg Ile Ile Asp Cys Ala Phe Thr Val Thr Phe Asn Pro Lys  
                                   260                                  265                                  270  
 Tyr Asp Thr Leu Leu Lys Ala Val Lys Asp Ala Thr Asn Thr Gly Ile  
                                   275                                  280                                  285  
 Lys Cys Ala Gly Ile Asp Val Arg Leu Cys Asp Val Gly Glu Ala Ile  
                                   290                                  295                                  300  
 Gln Glu Val Met Glu Ser Tyr Glu Val Glu Ile Asp Gly Lys Thr Tyr  
 305                                  310                                  315                                  320  
 Gln Val Lys Pro Ile Arg Asn Leu Asn Gly His Ser Ile Gly Gln Tyr  
                                   325                                  330                                  335  
 Arg Ile His Ala Gly Lys Thr Val Pro Ile Val Lys Gly Gly Glu Ala  
                                   340                                  345                                  350  
 Thr Arg Met Glu Glu Gly Glu Val Tyr Ala Ile Glu Thr Phe Gly Ser  
                                   355                                  360                                  365  
 Thr Gly Lys Gly Val Val His Asp Asp Met Glu Cys Ser His Tyr Met  
                                   370                                  375                                  380  
 Lys Asn Phe Asp Val Gly His Val Pro Ile Arg Leu Pro Arg Thr Lys  
 385                                  390                                  395                                  400  
 His Leu Leu Asn Val Ile Asn Glu Asn Phe Gly Thr Leu Ala Phe Cys  
                                   405                                  410                                  415  
 Arg Arg Trp Leu Asp Arg Leu Gly Glu Ser Lys Tyr Leu Met Ala Leu  
                                   420                                  425                                  430  
 Lys Asn Leu Cys Asp Leu Gly Ile Val Asp Pro Tyr Pro Pro Leu Cys  
                                   435                                  440                                  445  
 Asp Ile Lys Gly Ser Tyr Thr Ala Gln Phe Glu His Thr Ile Leu Leu  
                                   450                                  455                                  460  
 Arg Pro Thr Cys Lys Glu Val Val Ser Arg Gly Asp Asp Tyr  
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<210> 40  
 <211> 1183  
 <212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (0)...(0)

<223> n = a, t, c or g

<400> 40

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ttttccatgt	ggatatggca	aagaaggaga	cggctctggcg	gcttgaagaa	tttgacgat	240
ttgccagctt	tgaggctcaa	ggtgcattgg	ccaacatagc	tgtggacaaa	gccaacttgg	300
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tatggaatgc	cccatggggc	atctcttgtg	tacttattgt	ttaaggtttc	ctcaaactgn	1140
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<210> 41

<211> 254

<212> PRT

<213> Homo sapiens

<400> 41

Met	Ala	Ile	Ser	Gly	Val	Pro	Val	Leu	Gly	Phe	Phe	Ile	Ile	Ala	Val	
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Leu	Met	Ser	Ala	Gln	Glu	Ser	Trp	Ala	Ile	Lys	Glu	Glu	His	Val	Ile	
			20					25					30			
Ile	Gln	Ala	Glu	Phe	Tyr	Leu	Asn	Pro	Asp	Gln	Ser	Gly	Glu	Phe	Met	
	35					40					45					
Phe	Asp	Phe	Asp	Gly	Asp	Glu	Ile	Phe	His	Val	Asp	Met	Ala	Lys	Lys	
	50				55						60					
Glu	Thr	Val	Trp	Arg	Leu	Glu	Glu	Phe	Gly	Arg	Phe	Ala	Ser	Phe	Glu	
65				70					75					80		
Ala	Gln	Gly	Ala	Leu	Ala	Asn	Ile	Ala	Val	Asp	Lys	Ala	Asn	Leu	Glu	
			85					90						95		
Ile	Met	Thr	Lys	Arg	Ser	Asn	Tyr	Thr	Pro	Ile	Thr	Asn	Val	Pro	Pro	
	100							105					110			
Glu	Val	Thr	Val	Leu	Thr	Asn	Ser	Pro	Val	Glu	Leu	Arg	Glu	Pro	Asn	
	115					120						125				
Val	Leu	Ile	Cys	Phe	Ile	Asp	Lys	Phe	Thr	Pro	Pro	Val	Val	Asn	Val	
	130				135						140					
Thr	Trp	Leu	Arg	Asn	Gly	Lys	Pro	Val	Thr	Thr	Gly	Val	Ser	Glu	Thr	
145				150					155					160		
Val	Phe	Leu	Pro	Arg	Glu	Asp	His	Leu	Phe	Arg	Lys	Phe	His	Tyr	Leu	
			165					170						175		
Pro	Phe	Leu	Pro	Ser	Thr	Glu	Asp	Val	Tyr	Asp	Cys	Arg	Val	Glu	His	
		180						185					190			

Trp Gly Leu Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro  
           195                                  200                                  205  
 Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu  
           210                                  215                                  220  
 Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys  
           225                                  230                                  235                                  240  
 Gly Val Arg Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu  
                                   245                                  250

<210> 42  
 <211> 266  
 <212> DNA  
 <213> Homo sapiens

<400> 42  
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 gggggccacg ctgagcacga aggcaaacc tactgcaacc acccctgcta cgcagccatg 180  
 tttgggccta aaggctttgg gcggggcgga gccgagagcc acactttcaa gtaaaccagg 240  
 tgggtggagac ccaccccttg ctgctt 266

<210> 43  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 43  
 Met Pro Lys Cys Pro Lys Cys Asn Lys Glu Val Tyr Phe Ala Glu Arg  
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 Val Thr Ser Leu Gly Lys Asp Trp His Arg Pro Cys Leu Lys Cys Glu  
           20                                  25                                  30  
 Lys Cys Gly Lys Thr Leu Thr Ser Gly Gly His Ala Glu His Glu Gly  
           35                                  40                                  45  
 Lys Pro Tyr Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys  
           50                                  55                                  60  
 Gly Phe Gly Arg Gly Gly Ala Glu Ser His Thr Phe Lys  
   65                                  70                                  75

<210> 44  
 <211> 1665  
 <212> DNA  
 <213> Homo sapiens

<400> 44  
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 cccgcgccct cgatcatcac agcatcatcg tggctgctct gggcggtgct ctgtccgtgg 480  
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 tgctttgctg caactgtcca cccgcacag acaagcctta ctccgccaag tattctgctg 780  
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 cggggccactg gctgctgggg actggggact gggcagagac tgagccaggc aggaaggcag 960

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cagccttcag cctctctggc ccactcggac aacttcccaa ggccgcctcc tgctagcaag 1020
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&lt;210&gt; 45

&lt;211&gt; 209

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 45

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Met Ala Ser Met Gly Leu Gln Val Met Gly Ile Ala Leu Ala Val Leu
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Gly Trp Leu Ala Val Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val
20     25     30
Thr Ala Phe Ile Gly Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu
35     40     45
Gly Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys
50     55     60
Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala
65     70     75     80
Arg Ala Leu Val Ile Ile Ser Ile Ile Val Ala Ala Leu Gly Val Leu
85     90     95
Leu Ser Val Val Gly Gly Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser
100    105    110
Ala Lys Ala Lys Thr Met Ile Val Ala Gly Val Val Phe Leu Leu Ala
115    120    125
Gly Leu Met Val Ile Val Pro Val Ser Trp Thr Ala His Asn Ile Ile
130    135    140
Gln Asp Phe Tyr Asn Pro Leu Val Ala Ser Gly Gln Lys Arg Glu Met
145    150    155    160
Gly Ala Ser Leu Tyr Val Gly Trp Ala Ala Ser Gly Leu Leu Leu Leu
165    170    175
Gly Gly Gly Leu Leu Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro
180    185    190
Tyr Ser Ala Lys Tyr Ser Ala Ala Arg Ser Ala Ala Ala Ser Asn Tyr
195    200    205
Val

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&lt;210&gt; 46

&lt;211&gt; 1009

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 46

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gtaactgatg gacagccgag gcagcccctt aggcggctta ggcctcccct gtggagcatc 180
cctgagggcg actccggcca gcccgagtga tgcgatccaa agagcactcc cgggtaggaa 240
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acagtggctg aacaccggga aggaactggc acttggagtc cggacatctg aaacttggtg 360

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tggttttggg tttggtttga cctggccttg attctagata ctctgatttg gttttgattt 540
tggttttggg taaactgcaa gagtgtgtat gcccttttta cctgtttttt tgtttgtggc 600
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tatggtaact tctaactctg tggccttaga cagtctagtc caaaggcata aagaaagttt 960
gctttaaaaa aaaaaaaaaa gaatggttat cttcaaaaaa aaaaaaaaaa 1009

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&lt;210&gt; 47

&lt;211&gt; 1250

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 47

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&lt;210&gt; 48

&lt;211&gt; 220

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

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Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly
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Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser
          20          25          30
Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly
          35          40          45
Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys
          50          55          60
Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg
65          70          75          80
Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val
          85          90          95
Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala
          100          105          110

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Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala  
           115                                  120                                  125  
 Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg  
           130                                  135                                  140  
 Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly  
           145                                  150                                  155                                  160  
 Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly  
                                   165                                  170                                  175  
 Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr  
                                   180                                  185                                  190  
 Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala  
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 Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val  
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<210> 49  
 <211> 3321  
 <212> DNA  
 <213> Homo sapiens

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 gaaaagaaac ttattttctgt tgacacggaa cattccaata tctatcttca aaatggccca 180  
 gatagaattg ggagactata taagaaggcc ctttatcttc agtacacaga tgaaaccttt 240  
 aggacaacta tagaaaaacc ggtctggcct gggtttttag gccctattat caaagctgaa 300  
 actggagata aagtttatgt acacttaaaa aaccttgcct ctaggcccta cacctttcat 360  
 tcacatggaa taacttacta taaggaacat gagggggcca tctaccctga taacaccaca 420  
 gattttcaaa gagcagatga caaagtatat ccaggagagc agtatacata catgttgctt 480  
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 aaaaaagatt ctctagataa agaaaaagaa aaacatattg accgagaatt tgtgggtgatg 660  
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 cagtctgagg attccacctt ctacctggga gagaggacat actatatcgc agcagtggag 2220  
 gtggaatggg attattcccc acaaagggag tgggaaaagg agctgcatca tttacaagag 2280  
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gacaccaaatt ctggctgaat gaaataaatt ggtgataagt ggaaaaaaga gaaaaaccaa 3240
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cattaaaga gactggagca t 3321

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&lt;210&gt; 50

&lt;211&gt; 1065

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

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Met Lys Ile Leu Ile Leu Gly Ile Phe Leu Phe Leu Cys Ser Thr Pro
  1           5           10           15
Ala Trp Ala Lys Glu Lys His Tyr Tyr Ile Gly Ile Ile Glu Thr Thr
  20           25           30
Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
  35           40           45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
  50           55           60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
  65           70           75           80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
  85           90           95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
  100          105          110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
  115          120          125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
  130          135          140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
  145          150          155          160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
  165          170          175          180
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
  180          185          190
Leu Ile Gly Pro Leu Ile Ile Cys Lys Lys Asp Ser Leu Asp Lys Glu
  195          200          205
Lys Glu Lys His Ile Asp Arg Glu Phe Val Val Met Phe Ser Val Val
  210          215          220
Asp Glu Asn Phe Ser Trp Tyr Leu Glu Asp Asn Ile Lys Thr Tyr Cys
  225          230          235          240
Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
  245          250          255
Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
  260          265          270
Leu Ser Met Cys Ala Glu Asp Arg Val Lys Trp Tyr Leu Phe Gly Met
  275          280          285

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Gly	Asn	Glu	Val	Asp	Val	His	Ala	Ala	Phe	Phe	His	Gly	Gln	Ala	Leu
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Thr	Asn	Lys	Asn	Tyr	Arg	Ile	Asp	Thr	Ile	Asn	Leu	Phe	Pro	Ala	Thr
305					310					315					320
Leu	Phe	Asp	Ala	Tyr	Met	Val	Ala	Gln	Asn	Pro	Gly	Glu	Trp	Met	Leu
				325					330					335	
Ser	Cys	Gln	Asn	Leu	Asn	His	Leu	Lys	Ala	Gly	Leu	Gln	Ala	Phe	Phe
			340					345					350		
Gln	Val	Gln	Glu	Cys	Asn	Lys	Ser	Ser	Ser	Lys	Asp	Asn	Ile	Arg	Gly
		355					360					365			
Lys	His	Val	Arg	His	Tyr	Tyr	Ile	Ala	Ala	Glu	Glu	Ile	Ile	Trp	Asn
	370					375					380				
Tyr	Ala	Pro	Ser	Gly	Ile	Asp	Ile	Phe	Thr	Lys	Glu	Asn	Leu	Thr	Ala
385					390					395					400
Pro	Gly	Ser	Asp	Ser	Ala	Val	Phe	Phe	Glu	Gln	Gly	Thr	Thr	Arg	Ile
				405					410					415	
Gly	Gly	Ser	Tyr	Lys	Lys	Leu	Val	Tyr	Arg	Glu	Tyr	Thr	Asp	Ala	Ser
			420					425					430		
Phe	Thr	Asn	Arg	Lys	Glu	Arg	Gly	Pro	Glu	Glu	Glu	His	Leu	Gly	Ile
		435					440					445			
Leu	Gly	Pro	Val	Ile	Trp	Ala	Glu	Val	Gly	Asp	Thr	Ile	Arg	Val	Thr
	450					455					460				
Phe	His	Asn	Lys	Gly	Ala	Tyr	Pro	Leu	Ser	Ile	Glu	Pro	Ile	Gly	Val
465					470					475					480
Arg	Phe	Asn	Lys	Asn	Asn	Glu	Gly	Thr	Tyr	Tyr	Ser	Pro	Asn	Tyr	Asn
				485					490					495	
Pro	Gln	Ser	Arg	Ser	Val	Pro	Pro	Ser	Ala	Ser	His	Val	Ala	Pro	Thr
			500					505					510		
Glu	Thr	Phe	Thr	Tyr	Glu	Trp	Thr	Val	Pro	Lys	Glu	Val	Gly	Pro	Thr
		515					520					525			
Asn	Ala	Asp	Pro	Val	Cys	Leu	Ala	Lys	Met	Tyr	Tyr	Ser	Ala	Val	Asp
	530					535					540				
Pro	Thr	Lys	Asp	Ile	Phe	Thr	Gly	Leu	Ile	Gly	Pro	Met	Lys	Ile	Cys
545					550					555					560
Lys	Lys	Gly	Ser	Leu	His	Ala	Asn	Gly	Arg	Gln	Lys	Asp	Val	Asp	Lys
				565					570					575	
Glu	Phe	Tyr	Leu	Phe	Pro	Thr	Val	Phe	Asp	Glu	Asn	Glu	Ser	Leu	Leu
			580					585					590		
Leu	Glu	Asp	Asn	Ile	Arg	Met	Phe	Thr	Thr	Ala	Pro	Asp	Gln	Val	Asp
		595					600					605			
Lys	Glu	Asp	Glu	Asp	Phe	Gln	Glu	Ser	Asn	Lys	Met	His	Ser	Met	Asn
	610					615					620				
Gly	Phe	Met	Tyr	Gly	Asn	Gln	Pro	Gly	Leu	Thr	Met	Cys	Lys	Gly	Asp
625					630					635					640
Ser	Val	Val	Trp	Tyr	Leu	Phe	Ser	Ala	Gly	Asn	Glu	Ala	Asp	Val	His
				645					650					655	
Gly	Ile	Tyr	Phe	Ser	Gly	Asn	Thr	Tyr	Leu	Trp	Arg	Gly	Glu	Arg	Arg
			660					665					670		
Asp	Thr	Ala	Asn	Leu	Phe	Pro	Gln	Thr	Ser	Leu	Thr	Leu	His	Met	Trp
		675					680						685		
Pro	Asp	Thr	Glu	Gly	Thr	Phe	Asn	Val	Glu	Cys	Leu	Thr	Thr	Asp	His
	690					695					700				
Tyr	Thr	Gly	Gly	Met	Lys	Gln	Lys	Tyr	Thr	Val	Asn	Gln	Cys	Arg	Arg
705					710					715					720
Gln	Ser	Glu	Asp	Ser	Thr	Phe	Tyr	Leu	Gly	Glu	Arg	Thr	Tyr	Tyr	Ile
				725					730					735	
Ala	Ala	Val	Glu	Val	Glu	Trp	Asp	Tyr	Ser	Pro	Gln	Arg	Glu	Trp	Glu
			740					745					750		
Lys	Glu	Leu	His	His	Leu	Gln	Glu	Gln	Asn	Val	Ser	Asn	Ala	Phe	Leu
		755					760						765		

Asp Lys Gly Glu Phe Tyr Ile Gly Ser Lys Tyr Lys Lys Val Val Tyr  
 770 775 780  
 Arg Gln Tyr Thr Asp Ser Thr Phe Arg Val Pro Val Glu Arg Lys Ala  
 785 790 795 800  
 Glu Glu Glu His Leu Gly Ile Leu Gly Pro Gln Leu His Ala Asp Val  
 805 810 815  
 Gly Asp Lys Val Lys Ile Ile Phe Lys Asn Met Ala Thr Arg Pro Tyr  
 820 825 830  
 Ser Ile His Ala His Gly Val Gln Thr Glu Ser Ser Thr Val Thr Pro  
 835 840 845  
 Thr Leu Pro Gly Glu Thr Leu Thr Tyr Val Trp Lys Ile Pro Glu Arg  
 850 855 860  
 Ser Gly Ala Gly Thr Glu Asp Ser Ala Cys Ile Pro Trp Ala Tyr Tyr  
 865 870 875 880  
 Ser Thr Val Asp Gln Val Lys Asp Leu Tyr Ser Gly Leu Ile Gly Pro  
 885 890 895  
 Leu Ile Val Cys Arg Arg Pro Tyr Leu Lys Val Phe Asn Pro Arg Arg  
 900 905 910  
 Lys Leu Glu Phe Ala Leu Leu Phe Leu Val Phe Asp Glu Asn Glu Ser  
 915 920 925  
 Trp Tyr Leu Asp Asp Asn Ile Lys Thr Tyr Ser Asp His Pro Glu Lys  
 930 935 940  
 Val Asn Lys Asp Asp Glu Glu Phe Ile Glu Ser Asn Lys Met His Ala  
 945 950 955 960  
 Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val  
 965 970 975  
 Gly Asp Glu Val Asn Trp Tyr Leu Met Gly Met Gly Asn Glu Ile Asp  
 980 985 990  
 Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg  
 995 1000 1005  
 Gly Val Tyr Ser Ser Asp Val Phe Asp Ile Phe Pro Gly Thr Tyr Gln  
 1010 1015 1020  
 Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys  
 1025 1030 1035 1040  
 His Val Thr Asp His Ile His Ala Gly Met Glu Thr Thr Tyr Thr Val  
 1045 1050 1055  
 Leu Gln Asn Glu Asp Thr Lys Ser Gly  
 1060 1065

&lt;210&gt; 51

&lt;211&gt; 1603

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

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<210> 52  
 <211> 226  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 <223> Xaa = any amino acid

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 His Gly Gly Ile Ser Gly Thr Ile Tyr Glu Tyr Gly Ala Leu Thr Ile  
 35 40 45  
 Asp Gly Glu Glu Tyr Ile Pro Phe Lys Gln Tyr Ala Gly Lys Tyr Val  
 50 55 60  
 Leu Phe Val Asn Val Ala Ser Tyr Xaa Gly Leu Thr Gly Gln Tyr Ile  
 65 70 75 80  
 Glu Leu Asn Ala Leu Gln Glu Glu Leu Ala Pro Phe Gly Leu Val Ile  
 85 90 95  
 Leu Gly Phe Pro Cys Asn Gln Phe Gly Lys Gln Glu Pro Gly Glu Asn  
 100 105 110  
 Ser Glu Ile Leu Pro Thr Leu Lys Tyr Val Arg Pro Gly Gly Gly Phe  
 115 120 125  
 Val Pro Asn Phe Gln Leu Phe Glu Lys Gly Asp Val Asn Gly Glu Lys  
 130 135 140  
 Glu Gln Lys Phe Tyr Thr Phe Leu Lys Asn Ser Cys Pro Pro Thr Ser  
 145 150 155 160  
 Glu Leu Leu Gly Thr Ser Asp Arg Leu Phe Trp Glu Pro Met Lys Val  
 165 170 175  
 His Asp Ile Arg Trp Asn Phe Glu Lys Phe Leu Val Gly Pro Asp Gly  
 180 185 190  
 Ile Pro Ile Met Arg Trp His His Arg Thr Thr Val Ser Asn Val Lys  
 195 200 205  
 Met Asp Ile Leu Ser Tyr Met Arg Arg Gln Ala Ala Leu Gly Val Lys  
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 Arg Lys  
 225

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 <211> 399  
 <212> DNA  
 <213> Homo sapiens

&lt;400&gt; 53

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&lt;210&gt; 54

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 54

Met	Lys	Ser	Ser	Gly	Leu	Phe	Pro	Phe	Leu	Val	Leu	Leu	Ala	Leu	Gly
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Thr	Leu	Ala	Pro	Trp	Ala	Val	Glu	Gly	Ser	Gly	Lys	Ser	Phe	Lys	Ala
			20					25					30		
Gly	Val	Cys	Pro	Pro	Lys	Lys	Ser	Ala	Gln	Cys	Leu	Arg	Tyr	Lys	Lys
		35					40					45			
Pro	Glu	Cys	Gln	Ser	Asp	Trp	Gln	Cys	Pro	Gly	Lys	Lys	Arg	Cys	Cys
	50					55					60				
Pro	Asp	Thr	Cys	Gly	Ile	Lys	Cys	Leu	Asp	Pro	Val	Asp	Thr	Pro	Asn
65					70					75				80	
Pro	Thr	Arg	Arg	Lys	Pro	Gly	Lys	Cys	Pro	Val	Thr	Tyr	Gly	Gln	Cys
				85					90					95	
Leu	Met	Leu	Asn	Pro	Pro	Asn	Phe	Cys	Glu	Met	Asp	Gly	Gln	Cys	Lys
			100					105					110		
Arg	Asp	Leu	Lys	Cys	Cys	Met	Gly	Met	Cys	Gly	Lys	Ser	Cys	Val	Ser
		115					120						125		
Pro	Val	Lys	Ala												
			130												

&lt;210&gt; 55

&lt;211&gt; 3557

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 55

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&lt;210&gt; 56

&lt;211&gt; 1148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 56

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20           25           30
Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp
35           40           45
Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr
50           55           60
Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly
65           70           75           80
Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
85           90           95

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Lys	Asn	Thr	Ser	Val	Gly	Pro	Leu	Tyr	Ser	Gly	Cys	Arg	Leu	Thr	Leu	165	170	175
Leu	Arg	Pro	Lys	Lys	Asp	Gly	Ala	Ala	Thr	Lys	Val	Asp	Ala	Ile	Cys	180	185	190
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Tyr	Trp	Glu	Leu	Ser	Gln	Leu	Thr	His	Ser	Ile	Thr	Glu	Leu	Gly	Pro	210	215	220
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Glu	Arg	Val	Leu	Gln	Gly	Leu	Leu	Arg	Ser	Leu	Phe	Lys	Ser	Thr	Ser	305	310	315
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Asp	Pro	Lys	Ser	Pro	Arg	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Trp	Glu	Leu	355	360	365
Ser	Gln	Leu	Thr	His	Asn	Ile	Thr	Glu	Leu	Gly	His	Tyr	Ala	Leu	Asp	370	375	380
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Ser	Gly	Ser	Arg	Leu	Thr	Leu	Leu	Arg	Pro	Glu	Lys	Asp	Gly	Glu	Ala	485	490	495
Thr	Gly	Val	Asp	Ala	Ile	Cys	Thr	His	Arg	Pro	Asp	Pro	Thr	Gly	Pro	500	505	510
Gly	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Leu	Glu	Leu	Ser	Gln	Leu	Thr	His	515	520	525
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Thr	Asp	Asn	Val	Met	Lys	His	Leu	Leu	Ser	Pro	Leu	Phe	Gln	Arg	Ser		
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Ser	Leu	Gly	Ala	Arg	Tyr	Thr	Gly	Cys	Arg	Val	Ile	Ala	Leu	Arg	Ser		
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Glu	Pro	Pro	Thr	Thr	Pro	Lys	Pro	Ala	Thr	Thr	Phe	Leu	Pro	Pro	Leu		
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Ser	Tyr	Phe	Ser	Asp	Cys	Gln	Val	Ser	Thr	Phe	Arg	Ser	Val	Pro	Asn		
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 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu  
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&lt;210&gt; 57

&lt;211&gt; 853

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 57

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&lt;210&gt; 58

&lt;211&gt; 125

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 58

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Asp	Arg	Lys	Met	Val	Gly	Asp	Val	Thr	Gly	Ala	Gln	Ala	Tyr	Ala	Ser
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Thr	Ala	Lys	Cys	Leu	Asn	Ile	Trp	Ala	Leu	Ile	Leu	Gly	Ile	Leu	Met
				85					90					95	
Thr	Ile	Gly	Phe	Ile	Leu	Ser	Leu	Val	Phe	Gly	Ser	Val	Thr	Val	Tyr
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His	Ile	Met	Leu	Gln	Ile	Ile	Gln	Glu	Lys	Arg	Gly	Tyr			
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&lt;210&gt; 59

&lt;211&gt; 1512

<212> DNA  
<213> Homo sapiens

<400> 59

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<210> 60  
<211> 416  
<212> PRT  
<213> Homo sapiens

<400> 60

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			20					25					30		
Glu	Arg	Lys	Thr	Leu	Leu	Ser	Asn	Leu	Glu	Glu	Ala	Lys	Lys	Lys	Lys
		35				40					45				
Glu	Asp	Ala	Leu	Asn	Glu	Thr	Arg	Glu	Ser	Glu	Thr	Lys	Leu	Lys	Glu
	50					55					60				
Leu	Pro	Gly	Val	Cys	Asn	Glu	Thr	Met	Met	Ala	Leu	Trp	Glu	Glu	Cys
65					70					75				80	
Lys	Pro	Cys	Leu	Lys	Gln	Thr	Cys	Met	Lys	Phe	Tyr	Ala	Arg	Val	Cys
			85					90						95	
Arg	Ser	Gly	Ser	Gly	Leu	Val	Gly	Arg	Gln	Leu	Glu	Glu	Phe	Leu	Asn
			100				105						110		
Gln	Ser	Ser	Pro	Phe	Tyr	Phe	Trp	Met	Asn	Gly	Asp	Arg	Ile	Asp	Ser
		115					120					125			
Leu	Leu	Glu	Asn	Asp	Arg	Gln	Gln	Thr	His	Met	Leu	Asp	Val	Met	Gln
		130				135					140				
Asp	His	Phe	Ser	Arg	Ala	Ser	Ser	Ile	Ile	Asp	Glu	Leu	Phe	Gln	Asp
145					150					155				160	
Arg	Phe	Phe	Thr	Arg	Glu	Pro	Gln	Asp	Thr	Tyr	His	Tyr	Leu	Pro	Phe
			165					170						175	

Ser Leu Pro His Arg Arg Pro His Phe Phe Phe Pro Lys Ser Arg Ile  
 180 185 190  
 Val Arg Ser Leu Met Pro Phe Ser Pro Tyr Glu Pro Leu Asn Phe His  
 195 200 205  
 Ala Met Phe Gln Pro Phe Leu Glu Met Ile His Glu Ala Gln Gln Ala  
 210 215 220  
 Met Asp Ile His Phe His Ser Pro Ala Phe Gln His Pro Pro Thr Glu  
 225 230 235 240  
 Phe Ile Arg Glu Gly Asp Asp Asp Arg Thr Val Cys Arg Glu Ile Arg  
 245 250 255  
 His Asn Ser Thr Gly Cys Leu Arg Met Lys Asp Gln Cys Asp Lys Cys  
 260 265 270  
 Arg Glu Ile Leu Ser Val Asp Cys Ser Thr Asn Asn Pro Ser Gln Ala  
 275 280 285  
 Lys Leu Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg Leu  
 290 295 300  
 Thr Arg Lys Tyr Asn Glu Leu Leu Lys Ser Tyr Gln Trp Lys Met Leu  
 305 310 315 320  
 Asn Thr Ser Ser Leu Leu Glu Gln Leu Asn Glu Gln Phe Asn Trp Val  
 325 330 335  
 Ser Arg Leu Ala Asn Leu Thr Gln Gly Glu Asp Gln Tyr Tyr Leu Arg  
 340 345 350  
 Val Thr Thr Val Ala Ser His Thr Ser Asp Ser Asp Val Pro Ser Gly  
 355 360 365  
 Val Thr Glu Val Val Val Lys Leu Phe Asp Ser Asp Pro Ile Thr Val  
 370 375 380  
 Thr Val Pro Val Glu Val Ser Arg Lys Asn Pro Lys Phe Met Glu Thr  
 385 390 395 400  
 Val Ala Glu Lys Ala Leu Gln Glu Tyr Arg Lys Lys His Arg Glu Glu  
 405 410 415

&lt;210&gt; 61

&lt;211&gt; 1564

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 61

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cgccgagaag	gccggagcgt	cgccaccta	acgcgagggc	ctccattgcg	cgtgcgcgtt	120
gaggggcttc	ccgcaccta	tcgcgagacc	ccaacggctg	gtggcgctcg	ctgcgcgggc	180
gtccccacac	tgccggtccg	gaaaggcgac	ttccgggggc	tttggcacct	ggcggacgct	240
cccggagcgt	cgccaccta	acgcgagggc	ctccattgcg	cgtgcgcgtt	gaggggcttc	300
ccgcaccta	tcgcgagacc	ccaacggctg	gtggcgctcg	ctgcgcgtct	cggctgagct	360
ggccatggcg	cacctgtgcg	ggctgagggc	gagccggggc	tttctcgccc	tgctgggatc	420
gctgctcctc	tctgggggtcc	tggcgccga	ccgagaacgc	agcatccacg	acttctgcct	480
ggtgtcgaag	gtggtgggca	gatgccgggc	ctccatgcct	aagtgggtgg	acaatgtcac	540
tgacggatcc	tgccagctgt	ttgtgtatgg	gggctgtgac	ggaaacagca	ataattacct	600
gaccaaggag	gagtgcctca	agaaatgtgc	cactgtcaca	gagaatgcc	cgggtgacct	660
ggccaccagc	aggaatgcag	cggattcctc	tgtcccaagt	gctcccagaa	ggcaggattc	720
tgaagaccac	tccagcgata	tgttcaacta	tgaagaatac	tgaccgcca	acgcagtcac	780
tgggccttgc	cgtgcatacct	tcccacgctg	gtactttgac	gtggagagga	actcctgcaa	840
taactttcatc	tatggaggct	gccggggcaa	taagaacagc	taccgctctg	aggaggcctg	900
catgctccgc	tgcttccgcc	agcaggagaa	tcctcccctg	ccccttggct	caaagggtgt	960
ggttctggcg	gggctgttcg	tgatggtgtt	gatcctcttc	ctgggagcct	ccatggtcta	1020
cctgatccgg	gtggcacgga	ggaaccagga	gcgtgccctg	cgcaccgtct	ggagctccgg	1080
acatgacaag	gagcagctgg	tgaagaacac	atatgtcctg	tgaccgccct	gtcgccaaga	1140
ggactgggga	agggagggga	gactatgtgt	gagctttttt	taaatagcgg	gattgactcg	1200
gatttgagtg	atcattaggg	ctgaggtgtg	tttctctggg	aggtaggacg	gctgcttctc	1260
ggtctggcag	ggatgggttt	gctttggaaa	tcctctagga	ggctcctcct	cgcattggcct	1320
gcagtctggc	agcagccccg	agttgtttcc	tcgctgatcg	atttctttcc	tccaggtaga	1380

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gttttcttttg cttatgttga attccattgc ctcttttctc atcacagaag tgatgttgga 1440
atcgtttctt ttgtttgtct gatttatggt ttttttaagt ataaacaaaa gttttttatt 1500
aacatctgaa agaaggaaag taaaatgtac aagttaata aaaaggggcc ttccccttta 1560
gaat 1564

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<210> 62  
 <211> 252  
 <212> PRT  
 <213> Homo sapiens

<400> 62

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Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
20      25      30
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
35      40      45
Ala Ser Met Pro Lys Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
50      55      60
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65      70      75      80
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
85      90      95
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100     105     110
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115     120     125
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130     135     140
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145     150     155     160
Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
165     170     175
Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
180     185     190
Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
195     200     205
Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
210     215     220
Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly His
225     230     235     240
Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
245     250

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<210> 63  
 <211> 1147  
 <212> DNA  
 <213> Homo sapiens

<400> 63

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acagagccgg agcccagact gcgccagcag accgagtggc agagcggcca gcgctgggaa 180
ctggcactgg gtcgcttttg ggattacctg cgctgggtgc agacactgtc tgagcaggtg 240
caggaggagc tgctcagctc ccaggtcacc caggaaactga gggcgctgat ggacgagacc 300
atgaaggagt tgaaggccta caaatcggaa ctggaggtaac aactgacccc ggtggcggag 360
gagacgcggg cacggctgtc caaggagctg caggcggcgc aggcccggtc gggcgcgggac 420
atggaggacg tgtgcggccg cctggtgcag taccgcggcg aggtgcaggc catgctcggc 480
cagagcaccg aggagctgcg ggtgcgcctc gcctccacc tcgcaagct gcgtaagcgg 540
ctcctccgcg atgccgatga cctgcagaag cgctggcag tgtaccaggc cggggcccg 600

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gagggcgccg	agcgcggcct	cagcgccatc	cgcgagcgcc	tggggcccct	ggtggaacag	660
ggccgcgtgc	gggcccgcac	tgtgggctcc	ctggccggcc	agccgctaca	ggagcgggcc	720
caggcctggg	gcgagcggct	gcgcgcgcgg	atggaggaga	tgggcagccg	gacccgcgac	780
cgcttggaag	aggtgaagga	gcaggtggcg	gaggtgcgcg	ccaagctgga	ggagcaggcc	840
cagcagatac	gcctgcaggc	cgaggccttc	caggccccgc	tcaagagctg	gttcgagccc	900
ctggtggaag	acatgcagcg	ccagtggggc	gggctggtgg	agaaggtgca	ggctgccctg	960
ggcaccagcg	ccgccccctgt	gcccagcgac	aatcactgaa	cgccgaagcc	tgacgccatg	1020
cgacccacag	ccaccccgctg	cctcctgcct	ccgcgcagcc	tgacagcgga	gaccctgtcc	1080
ccgccccagc	cgctcctctg	gggtggaccc	tagtttaata	aagattcacc	aagtttcacg	1140
caaaaaa						1147

&lt;210&gt; 64

&lt;211&gt; 317

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

Met	Lys	Val	Leu	Trp	Ala	Ala	Leu	Leu	Val	Thr	Phe	Leu	Ala	Gly	Cys
1				5					10					15	
Gln	Ala	Lys	Val	Glu	Gln	Ala	Val	Glu	Thr	Glu	Pro	Glu	Pro	Glu	Leu
			20					25					30		
Arg	Gln	Gln	Thr	Glu	Trp	Gln	Ser	Gly	Gln	Arg	Trp	Glu	Leu	Ala	Leu
		35					40					45			
Gly	Arg	Phe	Trp	Asp	Tyr	Leu	Arg	Trp	Val	Gln	Thr	Leu	Ser	Glu	Gln
	50					55				60					
Val	Gln	Glu	Glu	Leu	Leu	Ser	Ser	Gln	Val	Thr	Gln	Glu	Leu	Arg	Ala
65				70					75						80
Leu	Met	Asp	Glu	Thr	Met	Lys	Glu	Leu	Lys	Ala	Tyr	Lys	Ser	Glu	Leu
				85				90						95	
Glu	Glu	Gln	Leu	Thr	Pro	Val	Ala	Glu	Glu	Thr	Arg	Ala	Arg	Leu	Ser
			100					105					110		
Lys	Glu	Leu	Gln	Ala	Ala	Gln	Ala	Arg	Leu	Gly	Ala	Asp	Met	Glu	Asp
		115					120					125			
Val	Cys	Gly	Arg	Leu	Val	Gln	Tyr	Arg	Gly	Glu	Val	Gln	Ala	Met	Leu
	130					135					140				
Gly	Gln	Ser	Thr	Glu	Glu	Leu	Arg	Val	Arg	Leu	Ala	Ser	His	Leu	Arg
145				150					155					160	
Lys	Leu	Arg	Lys	Arg	Leu	Leu	Arg	Asp	Ala	Asp	Asp	Leu	Gln	Lys	Arg
				165				170						175	
Leu	Ala	Val	Tyr	Gln	Ala	Gly	Ala	Arg	Glu	Gly	Ala	Glu	Arg	Gly	Leu
			180				185						190		
Ser	Ala	Ile	Arg	Glu	Arg	Leu	Gly	Pro	Leu	Val	Glu	Gln	Gly	Arg	Val
		195				200						205			
Arg	Ala	Ala	Thr	Val	Gly	Ser	Leu	Ala	Gly	Gln	Pro	Leu	Gln	Glu	Arg
	210					215					220				
Ala	Gln	Ala	Trp	Gly	Glu	Arg	Leu	Arg	Ala	Arg	Met	Glu	Glu	Met	Gly
225				230					235					240	
Ser	Arg	Thr	Arg	Asp	Arg	Leu	Asp	Glu	Val	Lys	Glu	Gln	Val	Ala	Glu
				245				250						255	
Val	Arg	Ala	Lys	Leu	Glu	Glu	Gln	Ala	Gln	Gln	Ile	Arg	Leu	Gln	Ala
			260				265						270		
Glu	Ala	Phe	Gln	Ala	Arg	Leu	Lys	Ser	Trp	Phe	Glu	Pro	Leu	Val	Glu
		275				280					285				
Asp	Met	Gln	Arg	Gln	Trp	Ala	Gly	Leu	Val	Glu	Lys	Val	Gln	Ala	Ala
	290					295					300				
Val	Gly	Thr	Ser	Ala	Ala	Pro	Val	Pro	Ser	Asp	Asn	His			
305					310					315					

&lt;210&gt; 65

&lt;211&gt; 2493

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

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cccatccctc agaagttatt tggggagggtg acttcccctc tgttcccca gcttaccctc      180
aacaactttg aaacaaccac tgtgatcaca gtcccccacg gatacagggt gaagctcgtc      240
ttccagcagt ttgacctgga gccttctgaa ggctgttctt atgattatgt caagatctct      300
gctgataaga aaagcctggg gaggttctgt gggcaactgg gttctccact gggcaacccc      360
ccgggaaaga aggaatttat gtcccaaggg aacaagatgc tgctgacctt ccacacagac      420
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gctgtggacc ttgatgaatg tgcttcccgg agcaaatcag gggaggagga tccccagccc      540
cagtgccagc acctgtgtca caactacgtt ggaggctact tctgttctct cctgccagge      600
tatgagcttc aggaagacag gcattcctgc caggctgagt gcagcagcga gctgtacacg      660
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caaggctacc agctcataga ggggaaccag gtgctgcatt ccttcacagc tgtctgccag      1140
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gcccgtatcc agtactactg ccatgagcca tattacaaga tgcagaccag agctggcagc      1320
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actttttcca aataaagttt tatgagaat gcc

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&lt;210&gt; 66

&lt;211&gt; 705

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

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Gly Ser Ile Pro Ile Pro Gln Lys Leu Phe Gly Glu Val Thr Ser Pro
      20             25             30
Leu Phe Pro Lys Pro Tyr Pro Asn Asn Phe Glu Thr Thr Thr Val Ile
      35             40             45

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Thr	Val	Pro	Thr	Gly	Tyr	Arg	Val	Lys	Leu	Val	Phe	Gln	Gln	Phe	Asp
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Leu	Glu	Pro	Ser	Glu	Gly	Cys	Phe	Tyr	Asp	Tyr	Val	Lys	Ile	Ser	Ala
65				70						75					80
Asp	Lys	Lys	Ser	Leu	Gly	Arg	Phe	Cys	Gly	Gln	Leu	Gly	Ser	Pro	Leu
				85					90					95	
Gly	Asn	Pro	Pro	Gly	Lys	Lys	Glu	Phe	Met	Ser	Gln	Gly	Asn	Lys	Met
			100					105					110		
Leu	Leu	Thr	Phe	His	Thr	Asp	Phe	Ser	Asn	Glu	Glu	Asn	Gly	Thr	Ile
		115					120					125			
Met	Phe	Tyr	Lys	Gly	Phe	Leu	Ala	Tyr	Tyr	Gln	Ala	Val	Asp	Leu	Asp
	130					135					140				
Glu	Cys	Ala	Ser	Arg	Ser	Lys	Ser	Gly	Glu	Glu	Asp	Pro	Gln	Pro	Gln
145					150					155					160
Cys	Gln	His	Leu	Cys	His	Asn	Tyr	Val	Gly	Gly	Tyr	Phe	Cys	Ser	Cys
				165					170					175	
Arg	Pro	Gly	Tyr	Glu	Leu	Gln	Glu	Asp	Arg	His	Ser	Cys	Gln	Ala	Glu
			180					185					190		
Cys	Ser	Ser	Glu	Leu	Tyr	Thr	Glu	Ala	Ser	Gly	Tyr	Ile	Ser	Ser	Leu
		195					200					205			
Glu	Tyr	Pro	Arg	Ser	Tyr	Pro	Pro	Asp	Leu	Arg	Cys	Asn	Tyr	Ser	Ile
	210					215					220				
Arg	Val	Glu	Arg	Gly	Leu	Thr	Leu	His	Leu	Lys	Phe	Leu	Glu	Pro	Phe
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Asp	Ile	Asp	Asp	His	Gln	Gln	Val	His	Cys	Pro	Tyr	Asp	Gln	Leu	Gln
				245					250					255	
Ile	Tyr	Ala	Asn	Gly	Lys	Asn	Ile	Gly	Glu	Phe	Cys	Gly	Lys	Gln	Arg
			260					265					270		
Pro	Pro	Asp	Leu	Asp	Thr	Ser	Ser	Asn	Ala	Val	Asp	Leu	Leu	Phe	Phe
		275					280					285			
Thr	Asp	Glu	Ser	Gly	Asp	Ser	Arg	Gly	Trp	Lys	Leu	Arg	Tyr	Thr	Thr
	290					295					300				
Glu	Ile	Ile	Lys	Cys	Pro	Gln	Pro	Lys	Thr	Leu	Asp	Glu	Phe	Thr	Ile
305					310					315					320
Ile	Gln	Asn	Leu	Gln	Pro	Gln	Tyr	Gln	Phe	Arg	Asp	Tyr	Phe	Ile	Ala
				325					330					335	
Thr	Cys	Lys	Gln	Gly	Tyr	Gln	Leu	Ile	Glu	Gly	Asn	Gln	Val	Leu	His
			340					345					350		
Ser	Phe	Thr	Ala	Val	Cys	Gln	Asp	Asp	Gly	Thr	Trp	His	Arg	Ala	Met
	355						360					365			
Pro	Arg	Cys	Lys	Ile	Lys	Asp	Cys	Gly	Gln	Pro	Arg	Asn	Leu	Pro	Asn
	370					375					380				
Gly	Asp	Phe	Arg	Tyr	Thr	Thr	Met	Gly	Val	Asn	Thr	Tyr	Lys	Ala	
385					390				395					400	
Arg	Ile	Gln	Tyr	Tyr	Cys	His	Glu	Pro	Tyr	Tyr	Lys	Met	Gln	Thr	Arg
			405						410					415	
Ala	Gly	Ser	Arg	Glu	Ser	Glu	Gln	Gly	Val	Tyr	Thr	Cys	Thr	Ala	Gln
			420					425					430		
Gly	Ile	Trp	Lys	Asn	Glu	Gln	Lys	Gly	Glu	Lys	Ile	Pro	Arg	Cys	Leu
	435						440					445			
Pro	Val	Cys	Gly	Lys	Pro	Val	Asn	Pro	Val	Glu	Gln	Arg	Gln	Arg	Ile
	450					455					460				
Ile	Gly	Gly	Gln	Lys	Ala	Lys	Met	Gly	Asn	Phe	Pro	Trp	Gln	Val	Phe
465					470					475					480
Thr	Asn	Ile	His	Gly	Arg	Gly	Gly	Gly	Ala	Leu	Leu	Gly	Asp	Arg	Trp
				485					490					495	
Ile	Leu	Thr	Ala	Ala	His	Thr	Leu	Tyr	Pro	Lys	Glu	His	Glu	Ala	Gln
			500					505					510		
Ser	Asn	Ala	Ser	Leu	Asp	Val	Phe	Leu	Gly	His	Thr	Asn	Val	Glu	Glu
		515					520					525			



Leu Met Lys Leu Gly Asn His Pro Ile Arg Arg Val Ser Val His Pro  
 530 535 540  
 Asp Tyr Arg Gln Asp Glu Ser Tyr Asn Phe Glu Gly Asp Ile Ala Leu  
 545 550 555 560  
 Leu Glu Leu Glu Asn Ser Val Thr Leu Gly Pro Asn Leu Leu Pro Ile  
 565 570 575  
 Cys Leu Pro Asp Asn Asp Thr Phe Tyr Asp Leu Gly Leu Met Gly Tyr  
 580 585 590  
 Val Ser Gly Phe Gly Val Met Glu Glu Lys Ile Ala His Asp Leu Arg  
 595 600 605  
 Phe Val Arg Leu Pro Val Ala Asn Pro Gln Ala Cys Glu Asn Trp Leu  
 610 615 620  
 Arg Gly Lys Asn Arg Met Asp Val Phe Ser Gln Asn Met Phe Cys Ala  
 625 630 635 640  
 Gly His Pro Ser Leu Lys Gln Asp Ala Cys Gln Gly Asp Ser Gly Gly  
 645 650 655  
 Val Phe Ala Val Arg Asp Pro Asn Thr Asp Arg Trp Val Ala Thr Gly  
 660 665 670  
 Ile Val Ser Trp Gly Ile Gly Cys Ser Arg Gly Tyr Gly Phe Tyr Thr  
 675 680 685  
 Lys Val Leu Asn Tyr Val Asp Trp Ile Lys Lys Glu Met Glu Glu Glu  
 690 695 700  
 Asp  
 705

<210> 67  
 <211> 777  
 <212> DNA  
 <213> Homo sapiens

<400> 67  
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 tgcagtgggg tggaggcagg taagaaaaag tgctcggaga gctcggacag cggctccggg 180  
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 Glu Glu  
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&lt;210&gt; 69

&lt;211&gt; 2402

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 69

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&lt;210&gt; 70

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 <212> PRT  
 <213> Homo sapiens

<400> 70

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 Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr  
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&lt;211&gt; 5460

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 71

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Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
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Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
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Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
 85          90          95
Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
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Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln
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Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val
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Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala
165          170          175
Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
180          185          190
Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
195          200          205
Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
210          215          220
Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225          230          235          240
Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile
245          250          255
Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
260          265          270
Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
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Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
290          295          300
Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
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Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
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Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
340          345          350
Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
355          360          365

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Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly  
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 Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro  
 385 390 395 400  
 Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro  
 405 410 415  
 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly  
 420 425 430  
 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu  
 435 440 445  
 Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp  
 450 455 460  
 Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly  
 465 470 475 480  
 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro  
 485 490 495  
 Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro  
 500 505 510  
 Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly  
 515 520 525  
 Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly  
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 Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser  
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 Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly  
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 Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys  
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 Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly  
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 Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu  
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 645 650 655  
 Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly  
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 Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu  
 675 680 685  
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 690 695 700  
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 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp  
 740 745 750  
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 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser  
 835 840 845

Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly  
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 Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg  
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 Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly  
 995 1000 1005  
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 Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly  
 1045 1050 1055  
 Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro  
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 Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly  
 1090 1095 1100  
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 1125 1130 1135  
 Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly  
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 Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn  
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 Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu  
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 1250 1255 1260  
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 1265 1270 1275 1280  
 Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met  
 1285 1290 1295  
 Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg  
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 Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe  
 1315 1320 1325



Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu  
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 1345 1350 1355 1360  
 Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile  
 1365 1370 1375  
 Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu  
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 Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe  
 1395 1400 1405  
 Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp  
 1410 1415 1420  
 Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro  
 1425 1430 1435 1440  
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 <211> 1051  
 <212> DNA  
 <213> Homo sapiens

<400> 73  
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 <211> 153  
 <212> PRT  
 <213> Homo sapiens

<400> 74  
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 Phe Gly Gly Leu Val Trp Ile Leu Val Ala Ser Ser Leu Val Pro Trp  
 35 40 45  
 Pro Leu Val Gln Gly Trp Val Met Phe Val Ser Val Phe Cys Phe Val  
 50 55 60  
 Ala Thr Thr Thr Leu Ile Ile Leu Tyr Ile Ile Gly Ala His Gly Gly  
 65 70 75 80



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&lt;210&gt; 76

&lt;211&gt; 1366

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala Val Thr

1

5

10

15

Leu	Cys	Leu	Ala	Thr	Cys	Gln	Ser	Leu	Gln	Glu	Glu	Thr	Val	Arg	Lys
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Gly	Pro	Ala	Gly	Asp	Arg	Gly	Pro	Arg	Gly	Glu	Arg	Gly	Pro	Pro	Gly
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Pro	Pro	Gly	Arg	Asp	Gly	Glu	Asp	Gly	Pro	Thr	Gly	Pro	Pro	Gly	Pro
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Pro	Gly	Pro	Pro	Gly	Pro	Gly	Leu	Gly	Gly	Asn	Phe	Ala	Ala	Gln	
65				70				75						80	
Tyr	Asp	Gly	Lys	Gly	Val	Gly	Leu	Gly	Pro	Gly	Pro	Met	Gly	Leu	Met
			85					90					95		
Gly	Pro	Arg	Gly	Pro	Pro	Gly	Ala	Ala	Gly	Ala	Pro	Gly	Pro	Gln	Gly
		100					105					110			
Phe	Gln	Gly	Pro	Ala	Gly	Glu	Pro	Gly	Glu	Pro	Gly	Gln	Thr	Gly	Pro
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Ala	Gly	Ala	Arg	Gly	Pro	Ala	Gly	Pro	Pro	Gly	Lys	Ala	Gly	Glu	Asp
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Gly	His	Pro	Gly	Lys	Pro	Gly	Arg	Pro	Gly	Glu	Arg	Gly	Val	Val	Gly
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Pro	Gln	Gly	Ala	Arg	Gly	Phe	Pro	Gly	Thr	Pro	Gly	Leu	Pro	Gly	Phe
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	210				215					220					
Val	Gly	Ala	Pro	Gly	Pro	Ala	Gly	Ala	Arg	Gly	Ser	Asp	Gly	Ser	Val
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		260					265					270			
Ala	Gly	Pro	Thr	Gly	Pro	Ala	Gly	Pro	Arg	Gly	Glu	Val	Gly	Leu	Pro
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Leu	Thr	Gly	Ala	Lys	Gly	Ala	Ala	Gly	Leu	Pro	Gly	Val	Ala	Gly	Ala
305				310					315						320
Pro	Gly	Leu	Pro	Gly	Pro	Arg	Gly	Ile	Pro	Gly	Pro	Pro	Gly	Ala	Ala
			325					330						335	
Gly	Thr	Thr	Gly	Ala	Arg	Gly	Leu	Val	Gly	Glu	Pro	Gly	Pro	Ala	Gly
		340					345					350			
Ser	Lys	Gly	Glu	Ser	Gly	Asn	Lys	Gly	Glu	Pro	Gly	Ser	Ala	Gly	Pro
	355					360					365				
Gln	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Glu	Glu	Gly					

Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His  
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 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn  
 515 520 525  
 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly  
 530 535 540  
 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro  
 545 550 555 560  
 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His  
 565 570 575  
 Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly  
 580 585 590  
 Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser  
 595 600 605  
 Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro  
 610 615 620  
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 625 630 635 640  
 Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu  
 645 650 655  
 Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp  
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 Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val  
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Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala  
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 1075 1080 1085  
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 1090 1095 1100  
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 1105 1110 1115 1120  
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 1140 1145 1150  
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 1155 1160 1165  
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 1235 1240 1245  
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 1315 1320 1325  
 Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile  
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 Gly Pro Val Cys Phe Lys  
 1365

&lt;210&gt; 77

&lt;211&gt; 1082

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

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&lt;210&gt; 78

&lt;211&gt; 258

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

Met	Met	Val	Leu	Gln	Val	Ser	Ala	Ala	Pro	Arg	Thr	Val	Ala	Leu	Thr
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Ala	Leu	Leu	Met	Val	Leu	Leu	Thr	Ser	Val	Val	Gln	Gly	Arg	Ala	Thr
			20					25					30		
Pro	Glu	Asn	Tyr	Leu	Phe	Gln	Gly	Arg	Gln	Glu	Cys	Tyr	Ala	Phe	Asn
		35					40					45			
Gly	Thr	Gln	Arg	Phe	Leu	Glu	Arg	Tyr	Ile	Tyr	Asn	Arg	Glu	Glu	Phe
		50					55				60				
Ala	Arg	Phe	Asp	Ser	Asp	Val	Gly	Glu	Phe	Arg	Ala	Val	Thr	Glu	Leu
65					70					75					80
Gly	Arg	Pro	Ala	Ala	Glu	Tyr	Trp	Asn	Ser	Gln	Lys	Asp	Ile	Leu	Glu
				85					90					95	
Glu	Lys	Arg	Ala	Val	Pro	Asp	Arg	Met	Cys	Arg	His	Asn	Tyr	Glu	Leu
			100					105					110		
Gly	Gly	Pro	Met	Thr	Leu	Gln	Arg	Arg	Val	Gln	Pro	Arg	Val	Asn	Val
		115					120					125			
Ser	Pro	Ser	Lys	Lys	Gly	Pro	Leu	Gln	His	His	Asn	Leu	Leu	Val	Cys
		130				135					140				
His	Val	Thr	Asp	Phe	Tyr	Pro	Gly	Ser	Ile	Gln	Val	Arg	Trp	Phe	Leu
145					150					155					160
Asn	Gly	Gln	Glu	Glu	Thr	Ala	Gly	Val	Val	Ser	Thr	Asn	Leu	Ile	Arg
				165					170					175	
Asn	Gly	Asp	Trp	Thr	Phe	Gln	Ile	Leu	Val	Met	Leu	Glu	Met	Thr	Pro
		180						185					190		
Gln	Gln	Gly	Asp	Val	Tyr	Thr	Cys	Gln	Val	Glu	His	Thr	Ser	Leu	Asp
		195					200					205			
Ser	Pro	Val	Thr	Val	Glu	Trp	Lys	Ala	Gln	Ser	Asp	Ser	Ala	Arg	Ser
		210				215					220				
Lys	Thr	Leu	Thr	Gly	Ala	Gly	Gly	Phe	Val	Leu	Gly	Leu	Ile	Ile	Cys
225					230					235					240
Gly	Val	Gly	Ile	Phe	Met	His	Arg	Arg	Ser	Lys	Lys	Val	Gln	Arg	Gly
				245					250					255	
Ser	Ala														

&lt;210&gt; 79

&lt;211&gt; 996

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

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&lt;210&gt; 80

&lt;211&gt; 180

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile Gly Ile Leu Val Leu Leu
      20             25             30
Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
      35             40             45
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
      50             55             60
Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
      65             70             75             80
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
      85             90             95
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
      100            105            110
Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
      115            120            125
Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
      130            135            140
Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
      145            150            155            160
Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
      165            170            175
Ala Leu Leu Gln
      180

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&lt;210&gt; 81

&lt;211&gt; 4316

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 81

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60



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&lt;210&gt; 82

&lt;211&gt; 362

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 82

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 20          25          30
Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Tyr Ile Ala Val Glu Tyr
 35          40          45
Val Asp Asp Thr Gln Phe Leu Arg Phe Asp Ser Asp Ala Ala Ile Pro
 50          55          60
Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln Tyr
 65          70          75          80
Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp Arg
 85          90          95
Val Ala Leu Arg Asn Leu Leu Arg Arg Tyr Asn Gln Ser Glu Ala Gly
100          105          110
Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp Gly
115          120          125
Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp Tyr
130          135          140
Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Val
145          150          155          160
Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu Glu
165          170          175
Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg Tyr
180          185          190
Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys Ala
195          200          205
His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys
210          215          220
Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln Arg
225          230          235          240
Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro
245          250          255
Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Ser
260          265          270
Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro
275          280          285
Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile Pro
290          295          300
Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val Thr
305          310          315          320
Gly Ala Val Val Ala Val Met Trp Arg Lys Lys Ser Ser Asp Arg
325          330          335

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 Pro Gly Ala Lys Ser Ala Ala Gln Ala Ala Ala Gln Thr Asn Ser Asn  
 50 55 60  
 Ala Ala Gly Lys Gln Leu Arg Lys Glu Ser Gln Lys Asp Arg Lys Asn  
 65 70 75 80  
 Pro Leu Pro Pro Ser Val Gly Val Val Asp Lys Lys Glu Glu Thr Gln  
 85 90 95  
 Pro Pro Val Ala Leu Lys Lys Glu Gly Ile Arg Arg Val Gly Arg Arg  
 100 105 110  
 Pro Asp Gln Gln Leu Gln Gly Glu Gly Lys Ile Ile Asp Arg Arg Pro  
 115 120 125  
 Glu Arg Arg Pro Pro Arg Glu Arg Arg Phe Glu Lys Pro Leu Glu Glu  
 130 135 140  
 Lys Gly Glu Gly Gly Glu Phe Ser Val Asp Arg Pro Ile Ile Asp Arg  
 145 150 155 160  
 Pro Ile Arg Gly Arg Gly Gly Leu Gly Arg Gly Arg Gly Gly Arg Gly  
 165 170 175

Arg Gly Met Gly Arg Gly Asp Gly Phe Asp Ser Arg Gly Lys Arg Glu  
 180 185 190  
 Phe Asp Arg His Ser Gly Ser Asp Arg Ser Ser Phe Ser His Tyr Ser  
 195 200 205  
 Gly Leu Lys His Glu Asp Lys Arg Gly Gly Ser Gly Ser His Asn Trp  
 210 215 220  
 Gly Thr Val Lys Asp Glu Leu Thr Glu Ser Pro Lys Tyr Ile Gln Lys  
 225 230 235 240  
 Gln Ile Ser Tyr Asn Tyr Ser Asp Leu Asp Gln Ser Asn Val Thr Glu  
 245 250 255  
 Glu Thr Pro Glu Gly Glu Glu His His Pro Val Ala Asp Thr Glu Asn  
 260 265 270  
 Lys Glu Asn Glu Val Glu Glu Val Lys Glu Glu Gly Pro Lys Glu Met  
 275 280 285  
 Thr Leu Asp Glu Trp Lys Ala Ile Gln Asn Lys Asp Arg Ala Lys Val  
 290 295 300  
 Glu Phe Asn Ile Arg Lys Pro Asn Glu Gly Ala Asp Gly Gln Trp Lys  
 305 310 315 320  
 Lys Gly Phe Val Leu His Lys Ser Lys Ser Glu Glu Ala His Ala Glu  
 325 330 335  
 Asp Ser Val Met Asp His His Phe Arg Lys Pro Ala Asn Asp Ile Thr  
 340 345 350  
 Ser Gln Leu Glu Ile Asn Phe Gly Asp Leu Gly Arg Pro Gly Arg Gly  
 355 360 365  
 Gly Arg Gly Gly Arg Gly Gly Arg Gly Arg Gly Gly Arg Pro Asn Arg  
 370 375 380  
 Gly Ser Arg Thr Asp Lys Ser Ser Ala Ser Ala Pro Asp Val Asp Asp  
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 Pro Glu Ala Phe Pro Ala Leu Ala  
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 gcaactcaag acacctgcag cagggcgtaga gaaaaagtaa aagaccagta ttttcacatt 180  
 gccaggtacc agaaacacag aagactgaca cccgccactt aagtggggcc agggctggtg 240  
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 Ala Cys Leu Tyr Tyr Ser Tyr Cys Asn Ser Arg His Leu Gln Gln Gly  
 35 40 45  
 Val Arg Lys Ser Lys Arg Pro Val Phe Ser His Cys Gln Val Pro Glu  
 50 55 60  
 Thr Gln Lys Thr Asp Thr Arg His Leu Ser Gly Ala Arg Ala Gly Val  
 65 70 75 80  
 Cys Pro Cys Cys His Pro Asp Gly Leu Leu Ala Thr Met Arg Asp Leu  
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 Leu Gln Tyr Ile Ala Cys Phe Phe Ala Phe Phe Ser Ala Gly Phe Leu  
 100 105 110  
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 115 120 125  
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 Cys Phe Val Ala Gly Ala Thr Leu Leu Ile Ala Gly Thr Pro Gly Ile  
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<210> 144  
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&lt;213&gt; Homo sapiens

&lt;400&gt; 144

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&lt;210&gt; 145

&lt;211&gt; 10

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 145

cctgccccgc

10

&lt;210&gt; 146

&lt;211&gt; 4111

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 146

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&lt;211&gt; 689

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 147

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Lys Glu Thr Asn Lys Asn Asn Thr Glu Ala Pro Val Thr Lys Ile Glu
          35          40          45
Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr Glu
 50          55          60
Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile Lys
65          70          75          80
Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln Gly
          85          90          95
Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val Cys
          100          105          110
Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys Met
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Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu Leu
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Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser Ser
145          150          155          160
Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu Thr
          165          170          175
Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser
          180          185          190
Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser Glu
          195          200          205
Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp
          210          215          220
Leu Ser Leu Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr Leu
225          230          235          240
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Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe Thr Lys
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Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala Met Asn
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Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys Lys Thr
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Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr Ala Asn
305          310          315          320
Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn Trp Thr
          325          330          335
Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln His Ile
          340          345          350
Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile Leu Leu
          355          360          365
Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile Val Lys
          370          375          380
Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile Lys Lys
385          390          395          400
Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly Tyr
          405          410          415
Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser Ser
          420          425          430

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 450 455 460  
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 465 470 475 480  
 Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn Ile Ser  
 485 490 495  
 Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro Ile Arg  
 500 505 510  
 Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp Phe Ala  
 515 520 525  
 Val Phe Tyr Leu Ile Ile Phe Phe Leu Ile Pro Leu Thr Val Phe  
 530 535 540  
 Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly Val Pro  
 545 550 555 560  
 Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu Gln Ser  
 565 570 575  
 Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn Phe Leu  
 580 585 590  
 Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val Ser Lys  
 595 600 605  
 Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Cys Cys Cys Arg Val Cys  
 610 615 620  
 Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys Arg Cys  
 625 630 635 640  
 Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln Asp Val  
 645 650 655  
 Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser Arg Glu  
 660 665 670  
 Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys Thr Ala  
 675 680 685  
 Leu